



# ANNALS of SURGERY

A MONTHLY REVIEW OF SURGICAL SCIENCE AND PRACTICE

ALSO THE OFFICIAL PUBLICATION OF THE AMERICAN SURGICAL  
ASSOCIATION, THE SOUTHERN SURGICAL ASSOCIATION, PHILA-  
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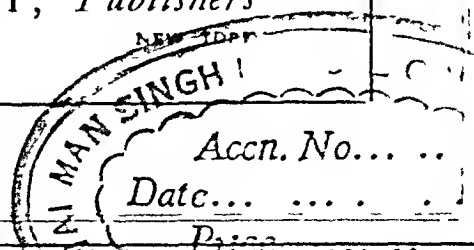
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## THE TREATMENT OF AIR FORCE COMBAT CASUALTIES

LT COL WILLIAM F MACFEE, MC

NEW YORK, N Y

IN A PERIOD of approximately seven months 198 officers and men of the United States Army Air Force were admitted as battle casualties to an Evacuation Hospital which was functioning as a fixed Station Hospital. Twenty-two of these had received definitive treatment in other hospitals. Treatment of the remaining 176 patients had been limited to first aid measures.

The great majority of casualties were caused by enemy gun fire. Other causes in order of frequency were freezing of fingers, toes, and other parts of the body, violent contact with parts of the plane or the earth's surface, burns, and anoxia.

The total number of casualties due to missiles was 141, and the enemy weapon responsible for the great majority was the 20-Mm aircraft cannon shell (Table I). Upon explosion these small shells throw out many small

TABLE I

NUMBER OF CASUALTIES PRODUCED BY THE VARIOUS TYPES OF MISSILES

Aircraft cannon shells 20-Mm	99
Machine gun bullets	17
Anti aircraft cannon shells	12
Secondary missiles from aeroplane	7
Unidentified missiles	5
Rocket shell	1
Total	141

fragments in all directions. If the explosion occurs at some distance the resulting wounds may be slight, but if the shell explodes nearby it is very destructive. In either case the numerous small fragments are a great danger to the eyes. Other missiles causing injury were, in order of frequency, machine gun bullets, anti-aircraft shell fragments, secondary missiles consisting of plane parts, unidentified missiles, and rocket shell fragments. At about the time rocket shells came into use there was a noticeable increase in the number of the wounded who did not know the source of the missile that had struck him. It is probable that some of these unidentified missiles were from rocket shells.

Twenty-two casualties were due to the freezing of various parts of the body at high altitude. These were transferred as soon as practicable to a



General Hospital where special studies of frostbite were being conducted. Two additional patients had severe wounds as well as frostbite.

Eight casualties were caused by violent contact with plane parts or the earth's surface, and in most instances were the result of forced landings or parachute jumps.

Burns, fortunately, were only three in number, and not severe.

There were two cases of anoxia, one of which was profound. After more than 24 hours of unconsciousness this patient began to show signs of orientation, and within a few days his recovery appeared to be complete.

The distribution of wounds with respect to the parts of the body involved is shown in Table II. The extremities were injured more frequently than other parts of the body. In this the historical pattern of war wounds is followed.

TABLE II

THE ANATOMIC DISTRIBUTION OF WOUNDS CAUSED BY MISSILES\*

I <i>Body as a whole</i>		IV <i>Injuries to Joints</i>	
Scalp	18	Elbow	2
Face	53	Knee	2
Eye	18	Ankle	1
Ear	2		
Neck	16	V <i>Nervous System</i>	
Shoulder region	23	Brain	5
Arm	37	Facial nerve	2
Forearm	20	Cervical plexus	1
Hand	16	Phrenic nerve	1
Chest wall	32	Brachial plexus	3
Abdominal wall	6	Ulnar nerve	4
Lumbar region	4	Medial antibrachial cutan	1
Gluteal region	13	Median nerve	4
Thigh	39	Radial nerve	4
Leg	25	Sacral plexus	1
Foot	11	Peroneal nerve	2
II <i>Fractures of Bones</i>		VI <i>Respiratory System</i>	
Skull	4	Pleura	1
Maxilla	1	Lung and pleura	7
Mandible	1		
Clavicle	1	VII <i>Digestive System</i>	
Humerus	4	Liver	3
Ulna	3	Small intestine	1
Radius	1	Colon	2
Phalanx manual	4	VIII <i>Genito urinary System</i>	
Metacarpal	8	Prepuce	1
Rib	3	Scrotum	1
Ilium	1	Bladder	1
Pubis	1		
Femur	3	IX <i>Circulatory System</i>	
Patella	1	Temporal artery	1
Tibia	5	Brachial artery	1
Tarsal	2	Radial artery	2
Metatarsal	5		
Phalanx, pedal	2		
III <i>Injuries to Tendons</i>			
Flexor tendons carpal	1		
Flexor tendon digital	2		

\* The figures indicate the number of times an anatomic part was injured and not the actual number of wounds.

After the extremities, the face came next in the order of wound frequency. In a total of 141 airmen wounded by gun fire, 53 (37.5 per cent) received wounds of the face. Among the patients with face wounds there were 18 eye injuries, approximately 12 per cent of the total number of 141 wounded. This is appreciably higher than the general incidence of eye injuries in World War I, which Matthews,<sup>1</sup> quoting Meisner, gives as 5 to 8 per cent.

The chest wall and scalp received numerous missiles but penetrations into the lungs and brain were relatively few. Wounds of the shoulder and gluteal regions were frequent, but as a rule not serious.

Compound fractures were fairly numerous. The fragments of aerial cannon shells were capable of fracturing the smaller bones, but had insufficient force to fracture a large bone unless the shell exploded nearby. The majority of fractures of the large bones were caused by heavier missiles.

The brain was damaged in five instances, but injuries to the nervous system concerned chiefly the peripheral nerves. A number of the nerve injuries were of a temporary nature, and probably due to contusion by secondary missiles arising from particles of tissue set in motion by the wounding agent. In some instances, however, long segments of important nerves were destroyed.

Wounds of the tendons, joints, digestive system, genito-urinary system, and the circulatory system were not numerous, but often were interesting and perplexing.

The treatment of wounds received in aerial combat was something in which none of the surgical staff was experienced, and there were no directives on this particular group of battle casualties. Many articles had been written on the treatment of wounds of the present war, but nearly all available information pertained to land or sea warfare. The opinion was virtually unanimous that the surgical measures should consist of thorough débridement, the application of a sulfonamide to all surfaces and recesses of the wound, packing with plain or medicated gauze, and immobilization of the injured part. The primary closure of wounds was mentioned but almost universally condemned.<sup>2-9</sup>

In the treatment of our earlier casualties we conformed to the general practice and treated all wounds by the open method. As a rule they healed well, and few became infected. The healing of open wounds by granulation, however, is a slow process, and it was obvious that much time might be saved by primary suture provided it was successful. In wounds as clean as these had proven to be, healing by primary union seemed a reasonable expectation.

Primary closures were first carried out in the more favorable cases and gradually extended to include the greater part of the wounds treated. Débridement and the application of sulfanilamide were done in the usual manner.

The results, which are shown in Table III, appear to have justified

this method of treatment Healing by primary union was obtained in 244 (95 per cent) of the total of 257 wounds that were closed Thirteen wounds (5 per cent) did not heal by primary union Nine of these (35 per cent) were reopened, or opened spontaneously, because of frank infection, three wound were reopened by the surgeon in the belief that they were infected, but cultures were negative, the edges of one uninfected wound separated because it had been closed under too much tension

TABLE III  
METHODS OF WOUND TREATMENT

Wounds debrided and closed	257
Subsequently infected	9
Subsequently reopened but not infected	4
Wounds closed by secondary suture	4
Subsequently infected	0
Subsequently reopened	0
Wounds closed but not debrided	3
Subsequently infected	3
Wounds debrided and left open	68
Subsequently infected	16

An investigation of subsequent results was made in all of the 244 wounds that had healed by primary union and it was found that none had broken down The investigation was conducted three to five months after the original closure of the wounds and was greatly facilitated by the cooperation of the Surgeons of the Air Force and the General Hospital to which some of the patients were evacuated

Secondary closure was done in four wounds Three of these were in patients transferred from other hospitals with open wounds, the fourth was one of our own patients All healed by primary union Secondary closure should be particularly useful as a planned procedure in certain fresh wounds which cannot be thoroughly débrided and in old wounds which have become relatively clean

Wounds débrided and left open were 68 in number, and 16 (235 per cent) of these subsequently developed infection It should be explained that the open method of treatment was reserved for wounds too large to permit closure, wounds which could not be débrided satisfactorily, and wounds which because of reduced vascularity were considered to have more than the usual susceptibility to infection The high incidence of infection in this group, therefore, cannot be attributed to the open method of treatment

Three wounds were sutured without debridement Two of these were wounds of the face in which preservation of tissue was a primary consideration, the third was a wound of the thigh which had been sutured at the Unit Dispensary The importance of débridement is emphasized by the fact that all of the three wounds sutured without débridement became infected

Infection led to serious consequences in only four of the entire series of cases One patient died of peritonitis four days after the suture of multiple

perforations of the ileum and cecum. Two patients had mid thigh amputation for gas gangrene, in both instances the infection developed in compound fractures of the bones of the leg, in one case the wound had been partially closed and lightly packed with vaselined gauze, in the other it had been left entirely open, one patient survived, the other succumbed 11 days after injury. The fourth serious infection occurred in a patient who had a large penetrating wound of the bladder. There was some urinary leakage after suture and an obstinate retroperitoneal infection developed. All other infections were of minor importance.

According to Lenoir<sup>10</sup> the primary suture of certain war wounds was started in 1915. He states that Lemaitre was able to carry out primary suture in 2,664 of 4,000 wounded, and the result was successful in 2,549 (95.6 per cent), but the cases for this procedure were selected with the greatest care. Primary suture was practiced to some extent by surgeons of the United States Army in World War I,<sup>11</sup> and when done under favorable circumstances good results were obtained.<sup>12</sup> Heuer,<sup>13</sup> working in an Evacuation Hospital near the front, was able to make primary closures on approximately 600 wounds, with success in 95 per cent. The 5 per cent of failures were wounds which subsequently showed evidence of infection, and were opened by removal of sutures.

In the present war the primary closure of wounds, as already stated, has been looked upon with disfavor in all the principal theaters of action. No doubt there are good reasons for this attitude, particularly with respect to ground troops. A number of considerations, however, serve to differentiate wounds sustained in the air from those received on the ground.

1. Bomber crews live under conditions which approach those of civilian life. They are comfortably housed, well fed, and have facilities to maintain cleanliness of body and clothing. The time between leaving the base and entering combat is a matter of a few hours at most, and the men go into action in good physical condition. None of these advantages obtain for the ground forces.

2. The missiles that inflict injury upon airmen are not grossly contaminated by earth, or other material from the earth's surface, and carry no foreign substances into the wounds except bits of clothing and occasionally secondary missiles derived from the plane itself.

3. Efficient first aid treatment, which includes the use of sulfanilamide, is administered in the plane immediately after injury, and as soon as the wounded arrive at the air field the medical personnel carry out whatever measures are necessary to assure their arrival at the hospital in the best possible condition.

4. Wounded airmen usually receive definitive surgical treatment within four to six hours of the time of injury. Ground troops often must wait many hours or even days.

With these considerations before us, it is obvious that important differences exist between air and ground force casualties. In treating the wounds

FIG 1



FIG 2

FIG 1—*Case A* Appearance of leg upon admission to the hospital. The number and extent of wounds made satisfactory debridement impossible.  
FIG 2—*Case A* Roentgenogram of leg showing comminuted fractures of the tibia. Numerous shell fragments are scattered throughout the soft parts.

of aerial warfare these differences should be recognized and turned to advantage

Before leaving the subject of treatment something should be said about shock as observed in wounded airmen. In brief, it may be stated that profound shock was not encountered except in those who had bled profusely. Other factors productive of shock, such as dehydration, physical exhaustion, and prolonged anoxia of the tissues, did not appear to have been severe enough to make them important as causative agents. Treatment with plasma yielded best results when given in large amounts, but the improvement could hardly be called spectacular. As a rule, the blood pressure did not rise to a satisfactory level and the general response was only a partial recovery. It is questionable whether plasma administration gave much better results than might have been obtained with physiologic saline and glucose. Definite recovery from shock usually did not become evident until the patient had received a transfusion of whole blood, and the degree of recovery was proportional, in a general way, to the amount of blood given. The results conformed to what might be expected in shock of almost purely hemorrhagic origin.

TABLE IV  
SUMMARY OF RESULTS

Casualties produced by	Discharged to Duty	Transferred to other Hospitals	Died	Total
Missiles	104	35	2	141
Violent contact with plane parts or earth's surface	7	1	0	8
Frost	3	19	0	22
Burns	3	0	0	3
Anoxia	1	1	0	2
Total	118	56	2	176

A general summary of results obtained in the total series of 176 air force battle casualties is given in Table IV. It will be observed that 104, (73.7 per cent), of the 141 airmen wounded by missiles were returned to duty directly from the evacuation hospital, 35 (24.8 per cent), were transferred to other hospitals, and two (1.4 per cent), who have already been described, died of their wounds.

Some of the problems of treatment may be illustrated by three cases which for convenience are designated as A, B, and C.

#### ILLUSTRATIVE CASE REPORTS

**Case A**—This patient sustained multiple wounds of the soft tissues of the left leg and compound, comminuted fractures of the tibia (Figs 1 and 2). The fibula was intact. A tourniquet had been applied above the knee and was still in place upon admission to the hospital. In spite of this the patient had bled profusely and was in shock. The tourniquet was removed and pulsations were felt in the dorsalis pedis and posterior tibial arteries. The damage to the leg was so extensive that a thorough debridement of all

FIG 3



FIG 4



FIG 5



FIG 6

FIG 3—Case B Extensive laceration of cheek involving the lips and angle of the mouth. There was also a compound fracture of the mandible.

FIG 4—Case B Injury to the face as seen from the front.

FIG 5—Case B Appearance of face approximately two weeks after incomplete debridement and suture. There was slight infection and partial separation of the wound edges.

FIG 6—Case B Appearance approximately six weeks after injury. The result illustrates the advantages of conservative debridement and immediate repair of facial injuries.

wounds was out of the question. The circulation, however, appeared adequate and the innervation was not seriously disturbed.

A fairly satisfactory debridement was done on the larger wounds, microcrystalline sulfathiazole was instilled, and the leg and thigh were immobilized in plaster. None of the wounds were sutured. Sulfadiazine was given by mouth for eight days after operation, and progress seemed quite satisfactory. On the ninth day there was complaint of some pain in the leg which was relieved by loosening the encasement. On the tenth day there was some fever, the leg was moderately swollen but there was no crepitus. On the eleventh day there was increased swelling, profuse, serous discharge, and slight localized crepitus. After a large transfusion, a midthigh amputation was performed, but the patient succumbed the same day. A different result might have been obtained if the gas gangrene had been recognized earlier.

FIG 7

FIG 9



FIG 8

FIG 10

FIG 7—Case C. Appearance of left arm with multiple wounds prepared for debridement. The neurovascular trunk is visible in the depth of the large wound.

FIG 8—Case C. The wounds after debridement. A skin incision was made at the distal angle of the large wound to include the two smaller wounds seen in Figure 7. Skin excision was limited to a few millimeters of the wound edges.

FIG 9—Case C. Wounds immediately after primary suture. In spite of the large size of the wounds closure was effected without tension.

FIG 10—Case C. Appearance of wound immediately before removal of sutures. Healing was by primary union.

**Case B**—This patient was struck near the angle of the mouth by an enemy missile thought to be a machine gun bullet. Considerable damage was done to the soft parts of the face and there was a compound fracture of the mandible (Figs 3 and 4). In spite of these injuries and a deep wound of the right deltoid muscle, this pilot brought his fortress home and made a good landing.

A complete debridement of the facial wound would have left a large defect and extensive plastic procedures requiring months of hospitalization would have been necessary. Excision of tissue, therefore, was confined to the dry, blackened shreds which were in effect foreign bodies. The wound was then sutured with care as to anatomic relationships.



Healing was complicated by slight infection and partial separation of the wound edges (Fig 5), but the final result was relatively good (Fig 6)

**Case C**—In addition to other serious injuries this patient received a severe flesh wound of the left arm which involved destruction of a good part of the biceps muscle and the soft tissues of the medial surface of the arm (Fig 7) A segment of the ulnar nerve also had been shot away There were other smaller wounds of the anterior and medial surfaces of the arm and a shell fragment had punctured the brachial artery near the antecubital fossa After debridement had been completed (Fig 8), it was possible to close the wounds without tension (Fig 9) Healing was by primary union (Fig 10), and there was undoubtedly much less scar formation than would have resulted from open treatment Prompt healing made possible an early attempt at nerve repair and avoided the impediment of dense scar tissue

### CONCLUSIONS

1 The primary closure of wounds has obvious advantages when conditions are right for its use

2 The wounds of aerial combat are received under peculiarly favorable conditions and many of them can be débrided and closed with good prospect of primary healing In this series, 95 per cent of 257 wounds closed by primary suture healed without infection or separation of the wound edges

3 Primary suture should not be attempted in wounds that are too large to permit closure without tension, in wounds which, for some reason, cannot be débrided satisfactorily, nor in wounds where adequate vascularity is in doubt

4 Secondary wound closure is useful as a planned procedure in doubtful fresh wounds and in old wounds that have become relatively clean

5 The open treatment of wounds has almost universal indorsement in ground force casualties The indications for open wound treatment in air combat casualties are much more restricted, but it is the preferred method in certain types of injuries Open treatment, however, does not insure against gas gangrene and other serious infections

6 The different methods of treating wounds should be considered as complementary and not opposed to each other

7 The decision as to the closed or open treatment of wounds sustained in aerial combat should be governed by a consideration of the circumstances in the case and not wholly restricted by rule

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# WHOLE UPPER EXTREMITY TRANSPLANT FOR HUMAN BEINGS GENERAL PLANS OF PROCEDURE AND OPERATIVE TECHNIC\*

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TRANSPLANTATION of homologous extremities is not new The idea has probably occurred to innumerable surgeons, from one time to another, during the existence of surgery

With the tremendous number of casualties which have occurred, and will occur, in the present war, the feasibility of a whole limb transplant should again be considered Granted, prostheses have been highly perfected, but with all our modern mechanical skill no mechanism can begin to replace a hand One machine gun bullet can render a hand useless Many hands have already been observed with severe, completely disabling burns, shrapnel wounds, crush wounds, *etc* At the present time there is nothing to offer these men but partial compensation in the form of a veteran's income Hence, there exists a need for successful whole limb transplantation

As early as 1897, Halsted succeeded in transplanting the hind leg of a dog from one side to the other, leaving the principal artery intact until the various tissues sectioned had healed MacCallum, in studying inflammation, completely amputated an extremity and replaced it by anastomosing the blood vessels and bringing together muscles and skin In 1906, Carrel and Guthrie showed the feasibility of a whole extremity graft by transplanting a recently severed extremity from one dog onto the prepared stump of another They repeated this work on several occasions, and had such success that they considered the matter closed The procedure was certainly possible, they concluded, but it was not practicable There was no source for the grafts in human beings The number of people who would want, or need, such a transplant were too few

Accordingly, during the next few years, Doctor Carrel digressed from the idea of whole limb transplants and turned to experimenting with organ transplants, again attempting to reestablish normal blood circulation of the transplant in the recipient These experiments with kidneys of animals are quite familiar to everyone interested in the subject but have no remarkable connection with extremity transplants However, it was during these years that blood vessel surgery received additional attention Indeed, the techniques of handling and suturing blood vessels were one of the main contributions to surgery from this work On the other hand, the work was not conclusive enough to warrant kidney or extremity transplants in human beings, so that surgeons confined their grafts to those in which the blood supply was

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\* The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department

Illustrations for this article were made by William B McNett from Cadaver Dissections done by author at the Daniel Baugh Institute of Anatomy, Philadelphia, Penna

completely severed, such as skin, corneal, bone, and fascial grafts. The idea that homologous transplants are unsuccessful has evolved from these grafts. However, these grafts are actually not comparable at all, inasmuch as their original blood supply is destroyed after separation from the host. Complete revascularization has to occur before such grafts live. This naturally cannot apply where the blood supply is preserved.

It is important to note a few of the obstacles met with in performing transplants in which the blood supply is preserved. The first of these is infection. Infection is one of the largest factors in production of thrombosis in anastomosed blood vessels. Murphy felt that almost all of the thrombi which formed at the site of blood vessel anastomoses where the intima was undamaged could be attributed to infection in and around this site. Thromboses have been so common in blood vessel surgery that almost all repair of blood vessels has been discouraged. Some of this discouragement resulted from the sad commentary of Sir George Makins on the results of end-to-end arterial suture during World War I. De Takats, using no anticoagulants nor agents to combat infection, discouraged the excision of emboli from blood vessels after their establishment for more than ten hours. Even during this first ten hours he had only about 40 per cent success.

Today, however, the picture is more promising. To combat infection we have at least two large, relatively new, groups of antibacterial agents. The first group includes the sulfonamides. This group is more popular at present, is synthetic in origin and has its action, apparently, as a static poison to the bacteria attempting to metabolize the substance. The second group is that including tyrothricin, gramicidin, and penicillin. This field was opened up by Dubos in 1939, and includes natural products which seem to have inhibitive and lytic action directly on the bacteria. With these two groups, already infection is becoming less and less of a problem. Blood vessel surgery is achieving more success. Even grafts where the blood supply is not preserved are reported to take more frequently where control of infection has been attempted.

Thrombosis, another obstacle to preservation of blood supply in transplants, now has two relatively new and directly combative agents. In 1936, Best, Charles, and Scott obtained a purified barium salt of heparin. This heparin preparation is nontoxic to human beings in therapeutic doses and is effective in preventing thrombosis. Its only disadvantage is that of administration, which has to be done parenterally.

As a result of using heparin, Murray reports remarkable successes. He feels that the ten-hour limit for embolectomies no longer holds, and reports 17 successful embolectomies using heparin postoperatively. He also reports three successful end-to-end arterial anastomoses and three cases using venous grafts to bridge gaps between severed arteries. No aneurysmal complications nor thrombi occurred. On one occasion, in repairing a false aneurysm, a section of the vein which was involved in the aneurysmal clot was used.

The clot had to be scraped from the intima of the venous graft and valve cusps had to be removed. In spite of the extensive damage to the intima of the venous graft it remained patent and the graft was successful. Priestley, and his coworkers, at the Mayo Clinic report that heparin is of definite value in prevention and treatment of postoperative thrombosis and embolism. Jaques, and Perett feel that thrombi on intimal surface of veins from chemical or mechanical injury can be completely prevented by the proper use of heparin.

In 1941, Link and his associates isolated and synthesized the causative hemorrhagic agent in spoiled sweet clover disease of cattle, 3, 3'-methylenebis (4-hydroxycoumarin). This substance has been popularly termed dicoumarol. It is not only more economical, but in contrast to heparin has been found to be effective when taken orally. Like heparin, though, it does not appear to be toxic in therapeutic doses. However, it seems to have a latent period of 48 to 72 hours, during which time it is necessary to use heparin following blood vessel surgery. The action of heparin apparently is direct neutralization of the substance thrombokinase. In contrast, dicoumarin seems to act by preventing the liver from forming prothrombin and has no direct effect on the blood itself. The clinical experience of Lehmann, Meyer, Allen, Bingham, Barker, Waugh, and others, gives good evidence that dicoumarin is a valuable adjunct to heparin in the prevention of thrombosis and embolism.

Another problem met with in performing a whole limb transplant is the method of fixation utilized for holding the bony fragments in position. Since Stader presented the advantages of his reduction and external fixation splint to Shaar, Kreuz, and their associates, at the U. S. Naval Hospital in Philadelphia, in 1941, its use has become widespread. It is a strong and light-in-weight splint which permits complete control of bone fragments in all planes, as well as traction, impaction and fixation. The apparatus does not restrict circulation and allows early active motion which makes it highly advantageous for use in a whole limb transplant.

Still other problems arise. One is the decision at which level to undertake the surgical procedure. The level of choice appears to be at the junction of the middle and lower third of the arm. This site is chosen because the structures here are large enough to work with conveniently. There is a single bony shaft and the structures involved are relatively simple. Another problem concerns the availability of the donor for the recipient at the proper time. In the early development of this procedure a surgical team could be trained, working in a well-equipped, large city, base hospital, employing as a source extremities of civil or military casualties. Permits could be obtained where necessary. Those needing grafts could wait in the hospital and be available when the proper graft was obtained. Then, after the procedure has been perfected, such modifications might be developed so as to make it practicable in field hospitals or hospital ships.

Then, again, in time, a method of preserving the limbs for grafting by means of a mechanical heart-lung perfusion apparatus might be perfected,

though this would not be necessary at first. Preservation by refrigeration offers another field of investigation. Certainly the amputation of extremities using ice packing anesthesia is suggestive. Also is the theory that metabolism temporarily ceases at low temperatures as shown in the freezing treatment of malignancies. Carrel demonstrated that small blood vessel grafts after having been stored in saline at slightly above freezing temperature for several days, not only function, but often live in their new host.

The laity, of course, would have to be educated to the idea involved. They would have to be impressed by the fact that the transplant is a living one, not dead. Prostheses met considerable opposition in the early days, but now artificial limbs are accepted entities.

In summary, then, with the advent of the sulfonamides, heparin, dicoumarin, Stader splint, and many other modern medical and surgical developments, there is every chance that a whole limb transplant in man should be possible and successful. Its success should be preceded by animal experimentation and cadaver surgery. There is certainly a growing demand for this procedure. Many technical problems connected with whole limb transplantation will have to be solved as they are met. However, a tentative plan of procedure is being presented.

#### OPERATIVE PROCEDURE FOR UPPER EXTREMITY TRANSPLANT

##### I Preoperative

###### A Nursing duties

- 1 Scrub operative site well above and below region daily for two or three days, ending on the day of operation with sterile preparation
- 2 Usual nursing care

###### B Medical duties include

- 1 Supervision of preoperative medications
- 2 Usual preoperative examination to be sure recipient is in good enough condition for surgery

###### C Technician's duties include

- 1 Typing of recipient's and donor's blood
- 2 Serologic complement-fixation or flocculation tests on each
- 3 Any other laboratory tests as deemed necessary by medical staff

##### II Operative

###### A Assistant surgeons

- 1 Prepare sterile field
- 2 Aid in surgical procedure as directed by surgeon

###### B Nurses or trained corpsmen

- 1 Manage instruments, drapes, solutions, *etc*
- 2 Maintain lighting properly

###### C Anesthetist gives appropriate anesthesia and handles intravenous solutions, medications, and transfusions

###### D Surgeon's procedure in preparing donor's graft (Fig 1)

After applying sterile Cohen tourniquet clamp, if necessary, a skin incision is made with unequal anterior and posterior flaps (Fig 4). The anterior flap comes to about one inch above the elbow crease, the posterior flap to the olecranon, the same as in recipient. An attempt is made to isolate the brachial cephalic and basilic veins superficially. They should be dissected free and tributaries ligated close to the veins for about 6 cm. These veins should be transected at least 8 cm above the level of the humeral condyles. Careful handling of the distal ends of the veins is important in order to avoid injuring their intimal surfaces. They should be attached to cannulae which lead to a dependent reservoir. The deep veins are cannulated similarly when they are transected later. After securing superficial veins, the skin and subcutaneous tissues are mobilized above and below all around the arm thus exposing the biceps and triceps muscles in addition to small parts of the brachialis anticus, brachioradialis, and flexor and extensor groups of the forearm. During this cleaning process brachial and antibrachial cutaneous nerves should be isolated and transected in the upper part of the wound. A small tie can be placed around these small nerves in order to keep track of them. Later on the portion tied can be sacrificed before anastomosis is attempted. The biceps tendon may now be isolated and transected in Z-fashion just below the musculotendinous junction. To facilitate repair, the Z-cut must always be the same, as, for example, a Z rather than an S, approaching the tendon anteriorly.

With the biceps muscle retracted superiorly all the important nerves and vessels can be readily obtained. The brachial artery and veins should be isolated first. They may be cut across as far proximal as possible. The artery should be cannulated to a heparinized transfusion, through which is bubbling oxygen and in which is contained an antibacterial agent such as penicillin or a sulfonamide. The veins, if large enough may be drained as previously directed for the superficial ones. Blood perfuses the extremity continuously and is recirculated as rapidly as possible.

Close to the vessels is the median nerve, which is next in order. It also, is transected proximally. A suture should be placed through the nerve near the cut end in a frontal plane. The suture is tied and then sewed to the skin distally so as to retract the nerve from the field and yet keep it from becoming rotated about its longitudinal axis (Fig 1). The damaged portion of the nerve is later sacrificed before anastomosis. The radial nerve can usually be found between the brachialis and the brachioradialis muscles near the humerus. It and the ulnar nerves are handled as was the median. The ulnar nerve is usually anterior to the medial muscle fibers of the triceps.

With this much done the lower half pin-unit for the Stader apparatus should be applied. Ample clearance (about 1 inch) for the skin should be allowed between the plastic bar and the triceps muscle. The pins should be placed through the aponeurosis of the triceps as far distally as possible. Care should be exercised so as not to get in the joint nor the humeral epiphysis. When the pins are properly inserted, a Z-incision may be made

through the triceps down to the bone, nearly freeing the muscle and tendon from the pins. A technic for this Z-incision must be adopted consistent with the technic used in the biceps tendon so as to avoid mistakes and confusion. The shaft of the humerus must finally be exposed for a narrow band proximal to the Stader half pin-unit. To do this the brachialis and brachioradialis muscles may be transected at the proper level and loosened subperiosteally

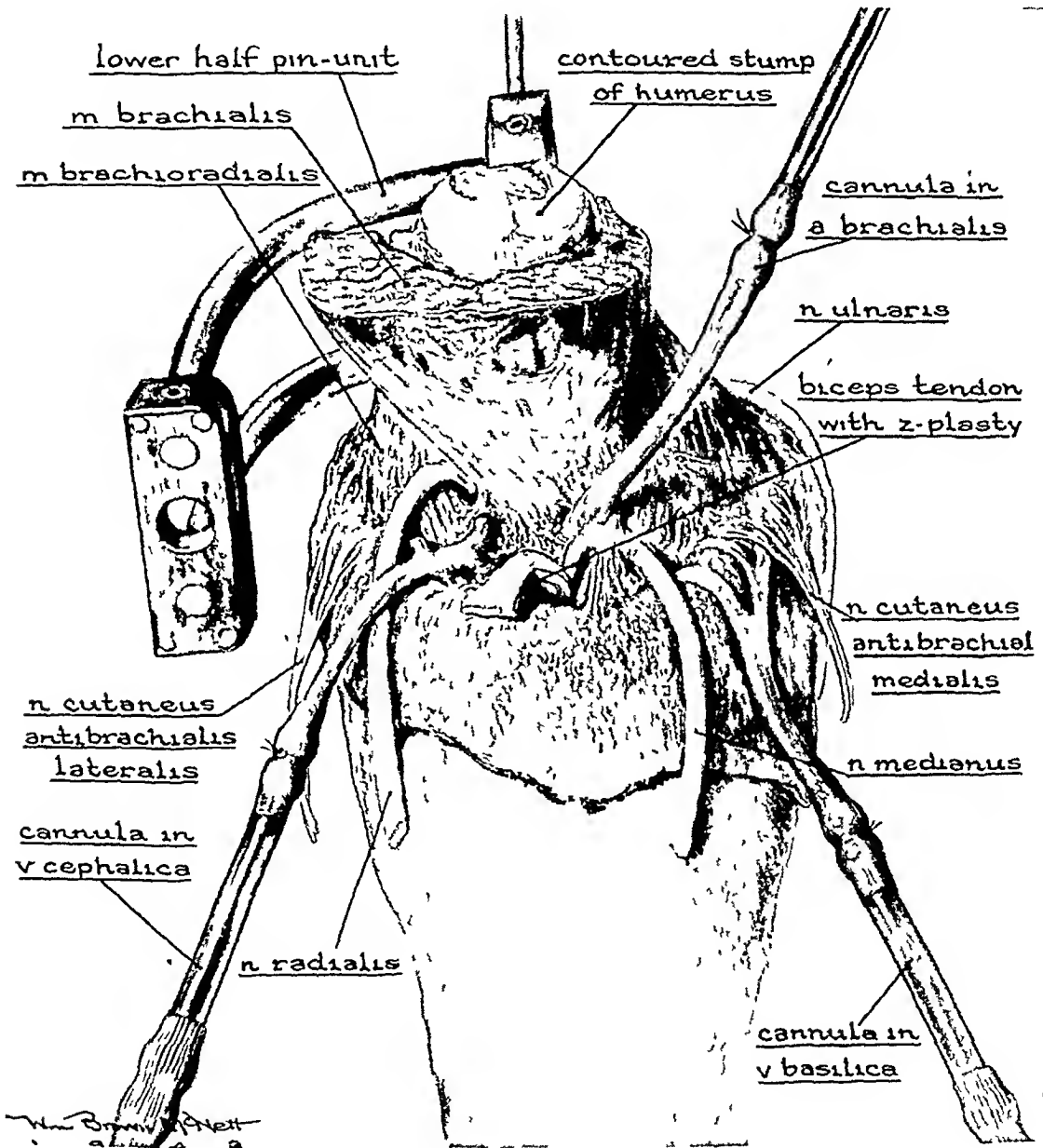


FIG. 1.—Preparation of the donor graft completed

along with the triceps in order to get adequate exposure. The humerus is finally cut at the junction of middle and lower thirds. Three saw cuts are made from the anterior, medial, and lateral edges of the humerus. The sawteeth point superiorly with the sawblade forming an acute angle with the distal humerus. The end-result is a three-sided cup in the proximal stump and a three-sided pencil tip in the distal fragment (Figs. 1 and 2).



The Stader pins may be used to help steady the arm while sawing. The extremity is finally draped with a sterile towel, and the surgeon takes the graft to the recipient or leaves it attached to perfusion solutions and oxygen tank for preservation. Ice packs may be applied also.

If necessary at this time, proximal stump of donor should be closed as after an amputation.

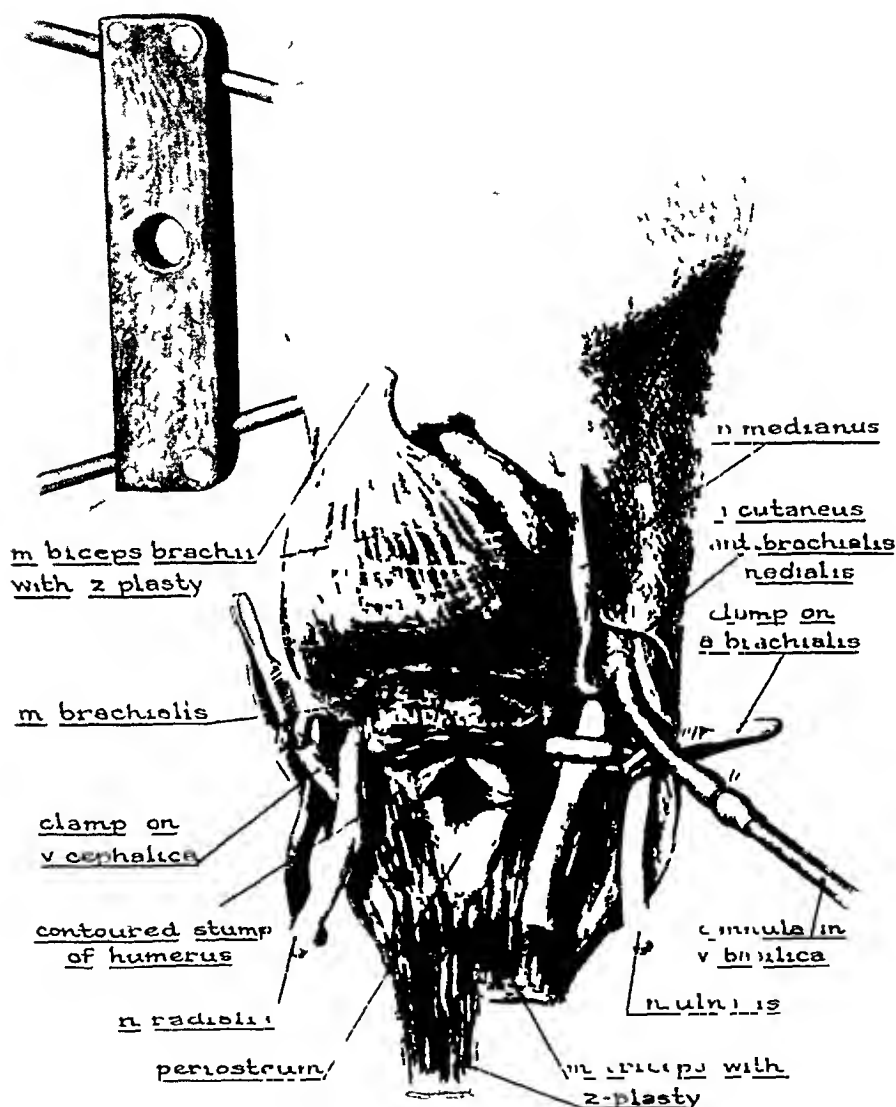


FIG 2—Preparation of the recipient for graft completed

### E Surgical Procedure in Preparing Recipient for Graft

Here, the upper Stader half pin-unit is applied first of all. Then after applying a sterile Cohen clamp, a skin incision is made exactly as in the donor. The superficial veins are cut as far distally as possible before large tributaries occur. Tendons and muscles are transected exactly as in the

donor Nerves are cut in the distal portion of the operating field and similarly tagged, reflecting them proximally. Before cutting the deep veins and the brachial artery, these vessels should be clamped proximally with a Crile or Spivack blood vessel clamp, being careful not to injure intimal surfaces. One of the larger veins may be cannulated for transfusion purposes. Finally, the humerus is transected in exactly the same manner as in the

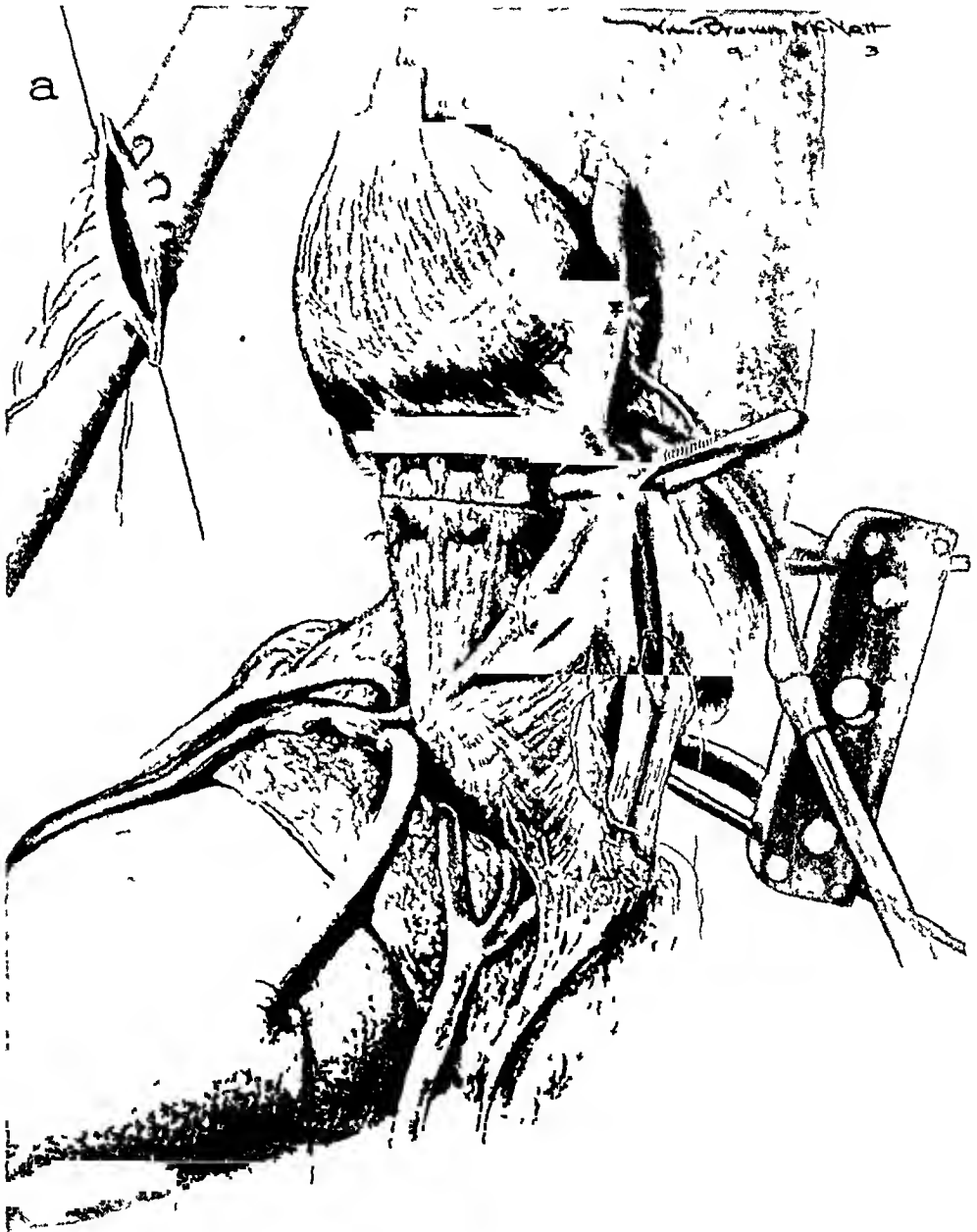


FIG. 3.—Donor graft in place on recipient, medial aspect. Closure partially completed.  
(1) Details of vascular anastomosis.

donor The distal, dismembered portion of recipient can be removed from the operating field.

#### F. Surgical Procedure in Approximating Graft

The donor arm must first be cut free from its cannulae and then brought into position. The Stader reduction and impaction bar should be attached

immediately To obtain perfect alignment some trimming of the bone ends may be necessary When alignment is obtained, bone ends are impacted and the apparatus is locked in position As the periosteum has been carefully preserved, its edges should be approximated with fine interrupted catgut sutures

All of the blood vessels larger than 3 Mm in diameter should be carefully trimmed in a diagonal manner and approximated by end-to-end anastomoses,

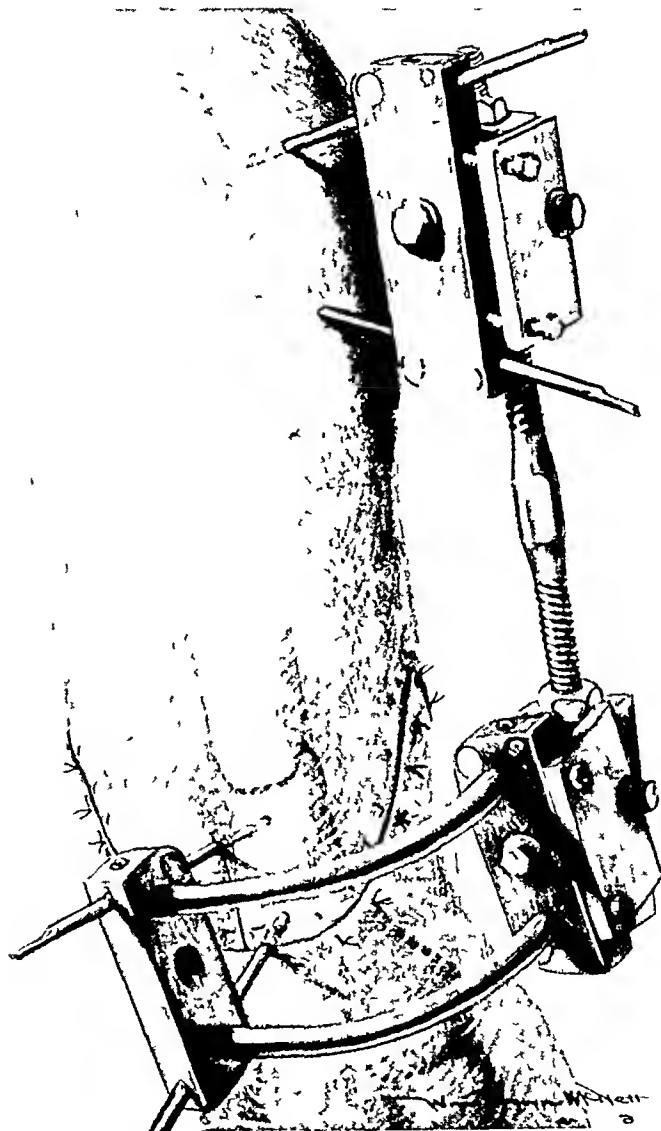


FIG 4—Graft approximated and wound closed, posterior aspect Relationship of numerus to Stader splint shown

using finest possible silk horizontal mattress sutures on a straight or curved, small, atraumatic needle (Fig 3a) These mattress sutures, when tied, evert the vascular intima After vessel anastomoses are completed the tourniquet should be removed and circulation restarted When the tourniquet has been removed any leakage around anastomoses should be stopped with a con-

tinuous stitch, or interrupted stitches, binding everted vascular edges together. Other minor hemostasis may be obtained by electrocoagulation or plain catgut ties. Nerves should be trimmed diagonally with a very sharp knife or razor blade, anastomosed, similarly to the blood vessels, uniting only the epineural sheaths in an everting manner. Anastomosing these structures with oblique transections permits a larger lumen when the scar tissue contracts months later.

Special care should be observed to unite all structures and especially nerves without rotating either end about longitudinal axes. Tendons are to be repaired in the manner of a Z-plasty. Muscle bellies transected must be approximated. No attention need be paid to approximating muscles to periosteum. Intermuscular septa may be repaired if convenient. Deep and superficial fascia and skin should be approximated with interrupted fine, absorbable sutures. Sulfanilamide powder should be dusted lightly in every layer of tissues before closure. A drain may be left in the anterior portion of the elbow for 24 hours if necessary.

### III Postoperative

A Apply sterile vaselined gauze or alcohol dressing

B Roentgenograms should be taken within 24 to 48 hours postoperatively, in order to check alignment and impaction of humeral fragments

C The extremity should be elevated until swelling disappears

D Patient should be thoroughly heparinized for two or three days, until dicoumarin has evidently become sufficiently effective to prevent thrombosis. Technician should check venous clotting and prothrombin time. Clotting time should be checked every six hours while heparin is being given and should be maintained at 15 minutes or longer. Prothrombin time should be checked daily. It may vary considerably but should be watched as an index of dicoumarin action and should not be allowed to get below 35 seconds. Heparin may be combatted with protamin, and dicoumarin with transfusions if at any time necessary.

E Medical Department to supervise administration of sulfa drugs and penicillin

F Physiotherapy should be started early possibly by the end of the first week or two. Bone ends should be impacted very slightly as needed.

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# STUDIES ON THE EFFECTS OF POSTURE IN SHOCK AND INJURY<sup>\*</sup>

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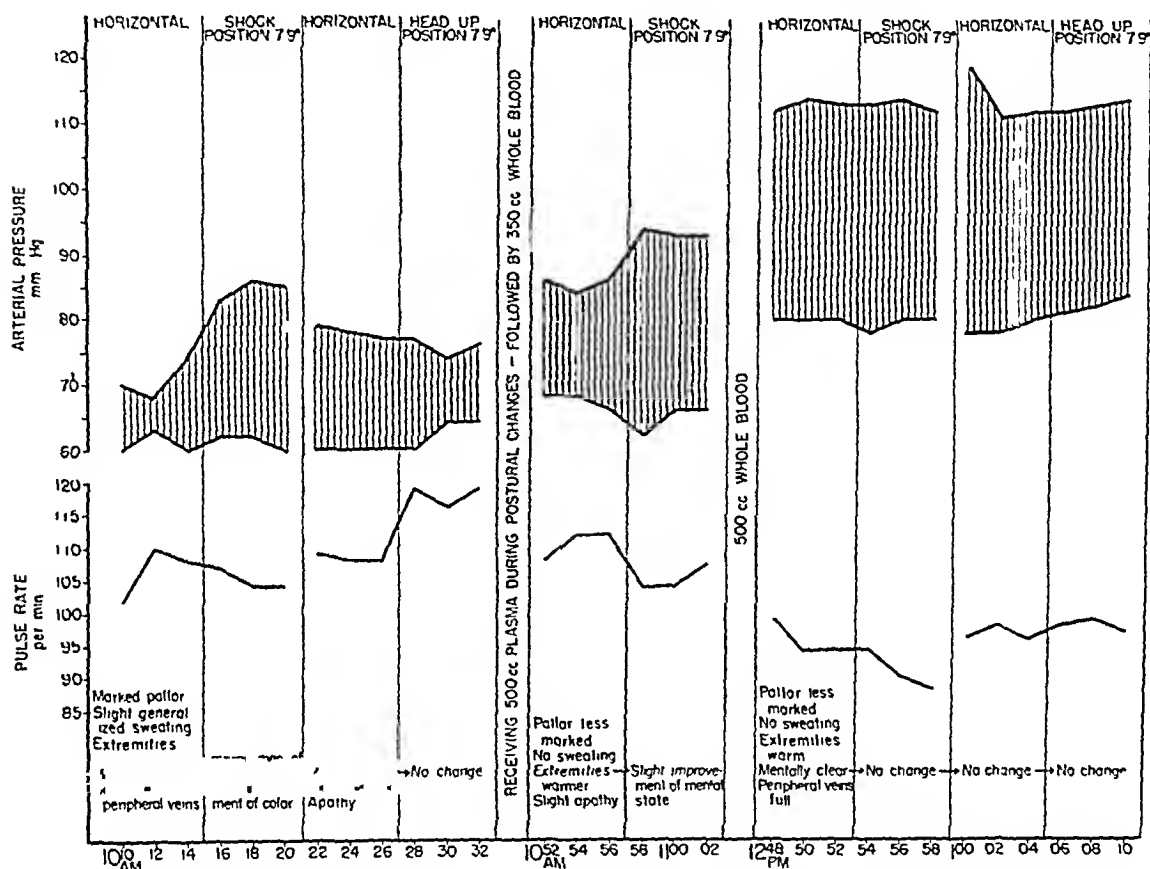
THE SHOCK OR FOOT-UP position rather than the horizontal or the head-up position is frequently employed in the treatment of shock or potential shock, but experimental evidence of the relative effects of these positions in injured persons is lacking. Widely different opinions have been expressed by various workers in this field as to the value of the shock position, but data presented have been based chiefly on animal experimentation or postural studies in normal persons. Hill<sup>1</sup> recommended its use in the treatment of shock on the basis of animal experiments. Henderson and Haggard<sup>2</sup> studied some of the cardiovascular effects of lowering the head of a normal person to an angle of 30 to 45 degrees. They concluded that the foot-up position would not be beneficial in shock. Cannon,<sup>3</sup> on the basis of his observations in World War I, stated that the shock position has no beneficial effect. From observations also made in the First World War, Porter<sup>4</sup> strongly recommended its use. Blalock<sup>5</sup> advocates the shock position because of the effect of gravity in aiding venous return to the heart and in aiding the circulation of the brain. Moon<sup>6</sup> states that posture can have no effect since the difficulty lies in the capillaries. Asmussen,<sup>7</sup> and his coworkers, after extensive studies on the effect of posture upon the circulation of the normal human being at an angle of 30 to 60 degrees in the foot-up and head-up positions state that the shock position may be beneficial in cases of circulatory insufficiency due to peripheral dilatation of vessels or to blood loss. Numerous other investigators have studied the effects of foot-up and head-up posture in normal persons at postural angles similar to those used by all of these investigators.

It was the purpose of this study to observe the effect of posture in patients with varying degrees of injury and shock both in the foot-up and head-up positions at angles similar to those produced by the shock blocks and the bed elevators used in most hospitals. These studies were continued by the senior author in collaboration with Dr Dickinson Richards, and his associates, at Bellevue Hospital, in a study of the effect of position upon cardiac output and other functions. Some of the cases included here were observed with this group (Tables II and IV) and will be reported elsewhere in greater detail in connection with other studies.

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<sup>\*</sup>The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Johns Hopkins University.

Patients were seen as early as possible after admission to the accident ward in the cases of injury or upon notification of the appearance of signs of shock in postoperative cases. A specimen of blood was obtained for determination of plasma protein and hematocrit values immediately before postural studies were begun and subsequent samples were obtained during the course of the study and at the end. In the patients listed in Tables II and IV, postural studies were begun during the latter part of the determina-



tion of blood volume or immediately thereafter. Symptoms and signs such as the presence or absence of sweating, pallor, the degree of consciousness, temperature of extremities to palpation and appearance of peripheral veins were observed and reported. Three readings of arterial pressure and pulse rate were made at two minute intervals and recorded. The patient was then placed immediately in the foot-up or shock position by elevation of the foot of the bed or examining table on shock blocks measuring 12 inches in height. The resulting angle measured approximately 7 to 9 degrees with the horizontal when the examining table or bed measured 6 to 7.5 feet in length. Because of the rapidity of the changes produced in some of the patients, observations on blood pressure, pulse rate, and other symptoms and signs were made at one minute, three minutes, and five minutes after the change in posture. The patient was immediately returned to the horizontal



TABLE II

EFFECTS OF POSTURAL CHANGE IN PATIENTS WITH MODERATE OR MARKED DIMINUTION OF BLOOD VOLUME

		(GROUP I)					Remarks
		Arterial Pressure		Pulse Rate	Blood Volume		
		Mm Hg			Sq M	B S A	
Name and Injury	Posture	(Cuff)	(Optical Manometer)	Per Min			
P P —Gunshot wound of abdomen Exposure	Flat	46/30	33/22	62	1320	2100	Arterial pressure rose immediately when placed in shock position but immediately began to drop
	Shock	60/40	39/25	83			Repeated 1½ hours later
	Flat	74/42	57/34	72			Had received 590 cc blood
	Foot up	86/61	71/37	75			1500 cc crystalloids Bleeding into peritoneal cavity
	Flat	88/66	76/44	78			Repeated 4 hours later
	Head up	88/60	74/43	76			Had received 1000 cc crys solution & 1300 cc blood
	Flat	110/58		78			Bleeding into peritoneal cavity 40 minutes later arterial pressure had dropped to 90/50 and other clinical signs of shock were present
	Shock	122/60		82			
	Flat	112/64		82			
W B —Crushing injury of chest Contusion of lung Hemothorax	Flat	135/89		116	1230	2230	
	Foot up	142/94		117			
	Flat	122/80		132	1160	1790	Repeated 5½ hours later
	Foot-up	144/90		128			Had received saline slowly Thirty minutes later patient showed evidence of clinical shock & was given 1000 cc whole blood
B S —Laceration of wrists & neck	Foot-up	126/80		116	1350	2180	Developed clinical picture of shock 15 minutes later
	Flat	110/70		120			30 minutes later No therapy
	Foot-up	81 (mean)					
	Flat	20 (mean)					
R C —Simple fract of femur	Flat	106/63	118/66	101	1170	2270	
	Foot up	107/65	116/64	90			
	Flat	95/64	98/57	101			
	Head up	101/65	110/64	102			
R M — Hemorrhage from esophageal varices	Flat	100/56		153	1810	2300	
	Foot up	108/59		150			
	Flat	105/58		162			
	Head up	101/61		164			
A R —Laceration of scalp	Flat		44/21	120	1030	1700	
	Foot-up		52/24	118			
	Flat	60/40	68/30	103			Repeated one hour later
	Foot-up	78/46	86/36	104			Had received 350 cc blood
	Flat	80/48	87/36	106			1500 cc N saline
	Flat	58/40	77/31	98	1800	2580	Repeated 1½ hours later
	Foot-up	60/40	78/31	100			after 100 cc blood & 1000 cc N saline
	Flat	55/40	66/27				
W B — Fracture of pelvis	Flat	67/42	54/26	112	1130	1670	
	Foot-up	66/41	49/25	114			
	Flat	61/30	53/27	120			
	Head-up	60/39	47/26	120			
	Flat	78/50	62/34	134			Repeated three hours later
	Foot up	86/50	66/33	132			Had received 900 cc blood 750 cc N saline
	Flat	95/53	78/40	120			Repeated 30 minutes later
	Foot-up	100/51	78/39	120	1520	2300	Had received 100 cc N saline Blood volume determination done one hour after postural studies Patient probably bleeding

position, after which similar observations were made at the same intervals. This procedure was then carried out in the head-up position, the same angle being used. The effects of both foot-up and head-up positions were repeatedly observed in most patients over a period of several hours. This procedure was followed in most instances, but occasionally because of therapeutic requirements, it could not be followed precisely.

Arterial pressure was determined in the patients listed in Tables I and III by the auscultatory method in the arm, and in the patients listed in Tables II and IV by both the auscultatory method in the brachial artery and the optical manometric method of Hamilton<sup>8</sup> in the femoral artery. In the determination of blood pressure in the arm, the arm was kept on the table or the bed parallel to the trunk in all postures. In the auscultatory method, care was taken to read the expiratory level of systolic pressure because respiratory variation in arterial pressure was frequently greatly increased. The first distinct change in Korotkow sounds was taken as the diastolic level. The heart rate was counted by arterial palpation or precordial auscultation or from the manometric tracings. Hematocrit levels were determined in duplicate with Wintrobe tubes. Plasma proteins were determined by the Barbour and Hamilton<sup>9</sup> method, the formula of Weech, Reeves and Goettsch<sup>10</sup> being used for translation of plasma specific gravity into plasma protein.

### RESULTS

For convenience of description, the cases observed will be divided into two groups on the basis of the clinical and laboratory evidence of shock and blood loss.

**GROUP I.** The patients comprising this group showed greater degrees of injury or hemorrhage. There were 16 patients in this group (Tables I and II) and clinical signs of shock were initially present or subsequently developed in all patients except one. The most frequently observed symptoms and signs were lowered arterial pressure, increase in pulse rate, decrease in pulse volume, various degrees of sweating and pallor, cool to cold extremities, diminished filling of peripheral veins, and narrowing of the field of consciousness. In the one patient who did not show definite clinical evidence of shock, a distinct fall in arterial pressure and other signs of

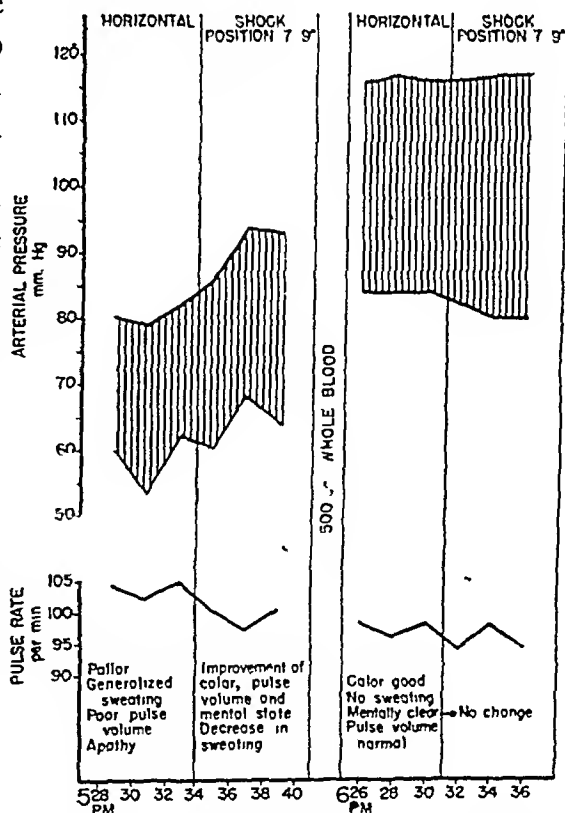
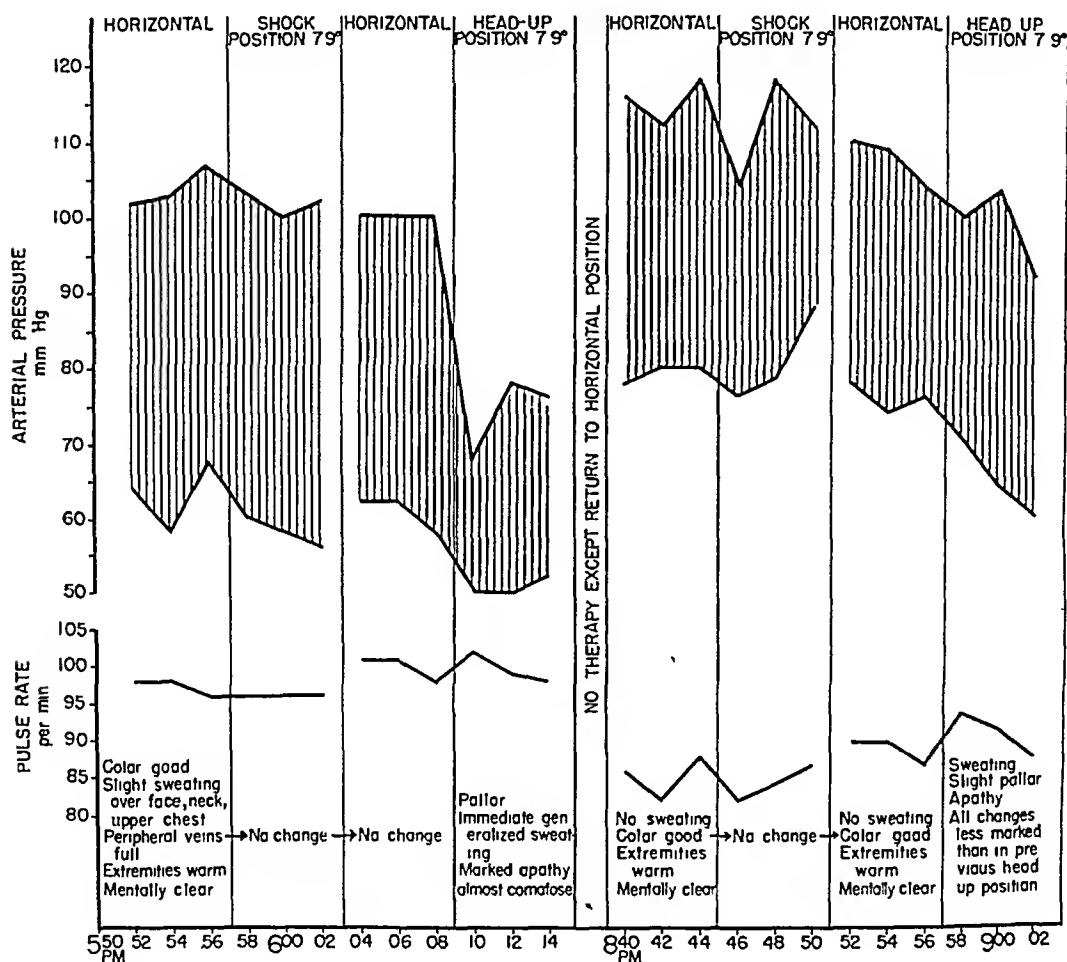


CHART 2—I L Effect of foot up position in patient in shock due to hemorrhage from lacerations

collapse were induced by postural change, and the nature of the injury and the blood studies indicate that he had considerable blood loss. This patient also showed a sharp decline in arterial pressure, bradycardia, sweating, and pallor during the passage of a urethral sound. In five patients the cause of shock was gastro-intestinal hemorrhage, skeletal trauma was responsible in four patients, soft-tissue laceration with hemorrhage in three, hemopneumothorax in two, gunshot wound of the abdomen in one, and severe hemorrhage occurring during a shoulder amputation in another. In the patients listed



CHAR. 3—W W Postural studies in patient with superficial lacerations of neck and arm. Pronounced fall in arterial pressure, sweating, pallor, and apathy occurred when head up position was assumed. No significant change was observed in foot up position. Symptoms and signs disappeared without intravenous therapy.

in Table I hematocrit levels were lowered in all except one, and plasma protein levels were lowered in two. The hematocrit level showed hemoconcentration in one patient (R. S.) while the plasma protein level was within normal range. In the patients listed in Table II, studies in blood volume showed moderate to marked diminution.

A difference in arterial pressure in the horizontal and the foot-up position was observed in all patients of this group except two. These two later showed

a difference in arterial pressure in the horizontal and the foot-up position after the blood volume had been partly replaced. The most frequent changes were observed in systolic pressure, ranging from 6 to 22 Mm Hg in the brachial artery and 6 to 18 Mm Hg in the femoral artery. In some patients the diastolic pressure rose significantly. The pulse rate slowed in several patients and showed moderate rise in one patient. In one patient (B S) a difference of 61 Mm Hg in mean arterial pressure in the two positions was observed.

TABLE IV  
EFFECTS OF POSTURAL CHANGE IN PATIENTS WITH SLIGHT DIMINUTION IN  
BLOOD VOLUME AND NORMAL CONTROLS

		(GROUP II) Arterial Pressure Mm Hg			Blood Volume	
Name and Injury	Posture	(Cliff)	(Optical	Pulse Rate Per Min	Sq M B S A	
		Brachial	Manometer) Femoral		Plasma	Blood
R W —Control	Flat	118/80	134/75	79	1620	2560
	Foot-up	119/80	138/73	75		
	Flat	120/84	139/76	78		
	Head-up	118/84	147/85	78		
S R —Compound fract of tibia and fibula	Flat	152/94	167/87	94	1780	3300
	Foot-up	152/90	171/91	98		
	Flat	150/90		96		
	Head-up	152/88		96		
A J —Stab wound of ab- dominal wall	Flat	108/74	117/71	86	1560	2690
	Foot-up	109/78	116/72	87		
	Flat	110/75	117/74	86		
	Head-up	108/80	127/79	89		
W H —Compound fract of tibia	Flat	130/73	154/71	77	1580	3040
	Foot-up	130/73	150/63	72		
	Flat	128/76	150/69	75		
	Head-up	125/70	151/74	74		
S R —Fracture of ribs Hemothorax	Flat	150/94		96	1530	2460
	Foot-up	150/94		94		
	Flat	150/90		94		
	Head-up	155/94		92		
I W —Intestinal obstruction	Flat	90/64	80/46	114	1580	2640
	Foot-up	91/61	78/41	109		
T M —Pneumonectomy	Flat	98/62		108	1560	2600
	Foot-up	100/62		116		
	Flat	97/62		104		
	Head-up	99/62		104		
I N —Control	Flat	122/73	155/73	47		
	Shock	121/76	148/69	47		
	Flat	122/74	152/72	48		
	Head-up	118/74	152/80	50		

Other changes were also evident when patients were placed in the foot-up position from the horizontal or returned from the foot-up position to the horizontal position. One of the most constant and striking of these observations was the improvement in mental state when the patient was placed in the foot-up position. Color and pulse volume frequently were seen to improve and sweating to diminish. The response of arterial

pressure and other findings to the foot-up position progressively diminished as the blood volume was replaced. Because of the condition of three patients, the initial arterial pressure was determined and other observations were made with the patients in the foot-up position, after which they were lowered to horizontal position and the observations repeated.

The effects of the head-up position were observed in nine patients of this group. In only three of these did significant fall in arterial pressure occur. In three patients the pulse rate rose 7 to 12 per minute but showed no noteworthy change in the remainder of the cases. Some patients who did not show a fall in arterial pressure when placed in head-up position showed a rise to above its previous level when returned to the horizontal position. No striking effect upon other signs and symptoms of these patients was noted. The head-up position was purposely avoided in some patients because of the condition of the patient and the evidence of vasomotor lability exhibited in other positions.

GROUP II Injury and blood loss were less severe in the patients of this group than in the preceding group. The clinical picture seen in the patients of Group I was not evident in this group, but some of the symptoms and physical signs were produced in several of these patients by postural change. In 14 patients (Tables III and IV) injury consisted of soft tissue laceration in three, multiple rib fracture in two, fracture of the sacrum due to gunshot wound in one, fracture of long bones in five, compound fracture of skull in one, one case of intestinal obstruction, and one patient who had undergone pneumonectomy and had received 1000 cc of blood during operation and whose blood volume was within normal range although arterial pressure was slightly lowered. Initially, the hematocrit and plasma protein levels were within normal range in the patients listed in Table III, however, evidence of hemodilution occurred in most instances between the initial and final specimens. In only three of these patients was replacement therapy carried out during the period of study, and in two of these three, treatment was given to determine its effect on postural change. In the third, replacement therapy was given because of lowered arterial pressure which persisted for approximately 12 hours in spite of treatment. This hypotension was probably related to the large quantity of alcohol which the patient had consumed during the preceding 24 hours.

The foot-up position produced a rise in systolic pressure of 10 Mm Hg in one patient of this group. Examination of the injured extremity in this patient showed pronounced swelling of the entire thigh and hemarthrosis of the knee. Repeated blood studies showed hemodilution. When the patient was again placed in the foot-up position a few minutes later, no change in arterial pressure was observed. Diastolic rises of 6 and 7 Mm Hg were observed in two patients and a fall of 8 Mm was noted in two others. No significant change in pulse rate was observed, and no significant change in other symptoms and signs was observed in patients of this group.

The head-up position produced striking results in some of the patients

of this group. A fall in arterial pressure occurred in seven of eight patients listed in Table III. The diastolic level fell from 4 to 60 Mm Hg in five patients, and the pulse rate rose 6 per minute in two patients and fell 4 and 6 per minute in two others. The greatest and most frequent changes in systolic pressure, ranging from 7 to 50 Mm Hg, were noted in six patients. In the seventh patient (J. P.), when the head-up position was assumed, the arterial pressure dropped precipitately to an unobtainable level, the radial pulse became impalpable, the precordial sounds became weak and distant, the heart rate slowed, the patient became comatose, pallor was evident, and sweating immediately became profuse and generalized. Upon resumption of the horizontal position the patient returned to his previous condition within a few minutes. Similar signs, including pallor, sweating, and narrowing of the field of consciousness, occurred in the other patients of this group who showed the greatest fall in arterial pressure in the head-up position. They also returned promptly to their previous state upon resumption of the horizontal position. In the patients listed in Table IV the changes in the head-up position were not so striking, a rise in femoral pressure was observed in one control and in one patient in whom the blood volume was only slightly diminished. The difference in the results obtained in the two groups may be related to the fact that the patients of Table II were seen earlier and observations were made earlier after injury. Five of the eight patients in Table III and two of those in Table IV had had alcohol before injury.

#### DISCUSSION

These observations would seem to be of both practical and theoretical interest. The position in which an injured patient is placed is an important consideration in the treatment of injuries since pronounced changes may be rapidly produced in either mild or severe injury by only slight alteration in posture. Differences in response to postural change were observed in mildly injured and more severely injured patients. When patients with injury and blood loss of moderate severity, or patients with severe injury and blood loss whose blood volume had been partly replaced, were put in the foot-up position, signs of improvement resulted. The most consistent effects noted were an increase in arterial pressure and improvement in mental state. Other signs of improvement, including diminution in sweating, improvement in color, increase in pulse volume, and decrease in pulse rate, were less constantly observed. The response of this group to head-up position was not so striking as in Group II, although its effect was not tried in all cases. The patients in the less severely injured group showed little or no response to foot-up position in most cases, but dramatic effects were observed in some of these patients when they were placed in the head-up position, resulting in, or approaching, a state of collapse or syncope, probably from vasodilatation and pooling of blood in dependent areas and resultant cerebral anemia. The condition is similar to the vasomotor collapse produced by Weiss<sup>11</sup> and

his associates by postural change following the administration of sodium nitrite. Alcohol was probably contributory in some cases, but three patients with acute alcoholism, without injury, have failed to show similar response.

Apparently, a state of vasomotor instability exists in the case of injury which was not found to be present in 20 normal controls and was seen to diminish and disappear in injured patients when they returned to normal. The degree of this vasomotor instability is indicated by the fact that the cardiovascular responses in these studies have been produced by relatively small postural angles as compared with the angles used by other investigators in studies in normal persons. The fact that the patients with the most severe injury and blood loss failed to show this rapid response until the blood volume had been partly replaced, suggests that vasoconstriction is more complete or constant and, therefore, less instability can be demonstrated by postural change. The angles used in this study are more likely to be encountered in the handling of injured patients during treatment or during various diagnostic procedures.

When it was observed that a difference in arterial pressure in the horizontal and the foot-up position was associated with diminution of blood volume and was not usually seen to occur in patients with less severe injuries and blood loss, attempt was made to utilize this observation as a test for blood loss and possibly for the diagnosis of preclinical or borderline shock. The persistence of this difference in arterial pressure, though diminishing until the blood volume has been replaced, might prove useful in determining when therapy was adequate, thereby conserving blood and plasma or preventing the reappearance of signs and symptoms of shock. Considerable emphasis has been placed upon the need for early diagnosis of shock because the picture from which the clinical diagnosis is usually made is relatively late. In three patients who subsequently developed the clinical picture of shock (B S, W B, R S) a definite difference in arterial pressure was observed in the horizontal and the foot-up position before the decline in arterial pressure and other signs of shock had appeared. In another patient (P P), who had received treatment and in whom clinical signs of shock had disappeared, intra-abdominal hemorrhage continued and a difference in arterial pressure in the two positions was demonstrated before the fall in arterial pressure and other signs of shock developed for the second time. This difference has not been observed thus far in patients with hypotension when the blood volume is normal, as evidenced by some of the cases in the accompanying tables. It has been stated in a preceding paragraph that no response in arterial pressure and in other signs was obtained in patients with the greatest diminution in blood volume until the blood volume has been partly replaced. Differences in arterial pressure in the horizontal and the foot-up position could obviously occur in patients seen soon after injury with evidence of so-called neurogenic shock since spontaneous rises in arterial pressure may occur. Similar changes might also be seen in any other patients with wide fluctuations in arterial

pressure Further studies will be required to prove the value of this lability of arterial pressure as an indication of borderline shock or adequacy of treatment in the case of frank shock These studies are being carried out at the present time

#### SUMMARY

1 The effect of postural change on thirty patients with various degrees of injury is described

2 Vasomotor instability was demonstrated in injured patients that was not present in normal controls and disappeared in injured patients when they returned to normal

3 Different effects were noted in response to the head-up or the foot-up position in mild and severe injury of hemorrhage

4 Some of the beneficial effects of the foot-up position in the treatment of shock or potential shock as well as some of the adverse effects observed in injured patients in the head-up position are described

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# OPERATION FOR ANEURYSM OF THE HEART

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I should like to report an operation for repair of aneurysm of the left ventricle of the heart. The operation consists of grafting a segment of fascia lata, or parietal pericardium, over the aneurysm for the purpose of preventing its rupture. This is the first operation of its kind, and it is felt that it should be reported.

There is nothing of a surgical nature in the literature on cardiac aneurysm except an operation for false aneurysm by Sauerbruch<sup>1</sup>. He made a diagnosis of mediastinal tumor but at operation found the tumor contained blood. The sac was opened. The cavity of the sac communicated with the right ventricle by an opening which could be felt by two fingers which were introduced through the opening into the heart to control bleeding. Ligatures were placed around the sac at the site of communication and as the fingers were withdrawn the ligatures were tied and hemorrhage was controlled. Excision of the sac was carried out. There was no statement concerning the presence of myocardium in the thin sac, and I assume that the sac was parietal pericardium. If this assumption is correct it is a false and not a true aneurysm. Excision of a true aneurysm of either ventricle of the heart appears to be an impractical procedure.

## EXPERIMENTS ON CARDIAC ANEURYSM

In 1934, I operated upon 16 dogs in an attempt to produce cardiac aneurysm. Some of these animals were kept for two to three years after operation but aneurysm was not produced and the experiments were not reported. Briefly, the procedure was to expose the heart and to open the auricle. A sphere of metal was introduced through the mitral valve into the ventricle. The myocardium was crushed between the sphere inside and the fingers outside the heart. It was possible to crush the myocardium to such a degree that one could recognize the color of the metal through epicardium and endocardium. The specimens showed a small amount of scar at the site of the contusion. Small deposits of calcium were also found. Pathologic manifestations of trauma were slight.<sup>2</sup>

Aneurysm of the human heart is usually produced by coronary artery occlusion. In our experiments in which occlusion of coronary artery was done a slight dilatation of the wall of the ventricle was occasionally observed but a well-developed aneurysm was never observed in these experiments. Hosler and Williams<sup>3</sup> produced an aneurysm of the right ventricle in one experiment by attaching ventricle to diaphragm. This was a true aneurysm and could be classified as a traction aneurysm.

## ANEURYSM OF HEART

### COMPRESSION SCARS ON THE HEART *versus* LOCALIZED AND GENERALIZED DILATATION OF THE HEART

Dakin's solution when introduced into the pericardial cavity of dogs is followed by the production of scar tissue in epicardium and parietal pericardium<sup>4, 5</sup> In the course of weeks or months the scar undergoes contraction and produces chronic compression of the heart<sup>6</sup> The chief point of interest in these experiments concerned the physiology of compression and the surgical problems of removing compression scars However, there is another aspect to this work which is new, which has not been discussed,

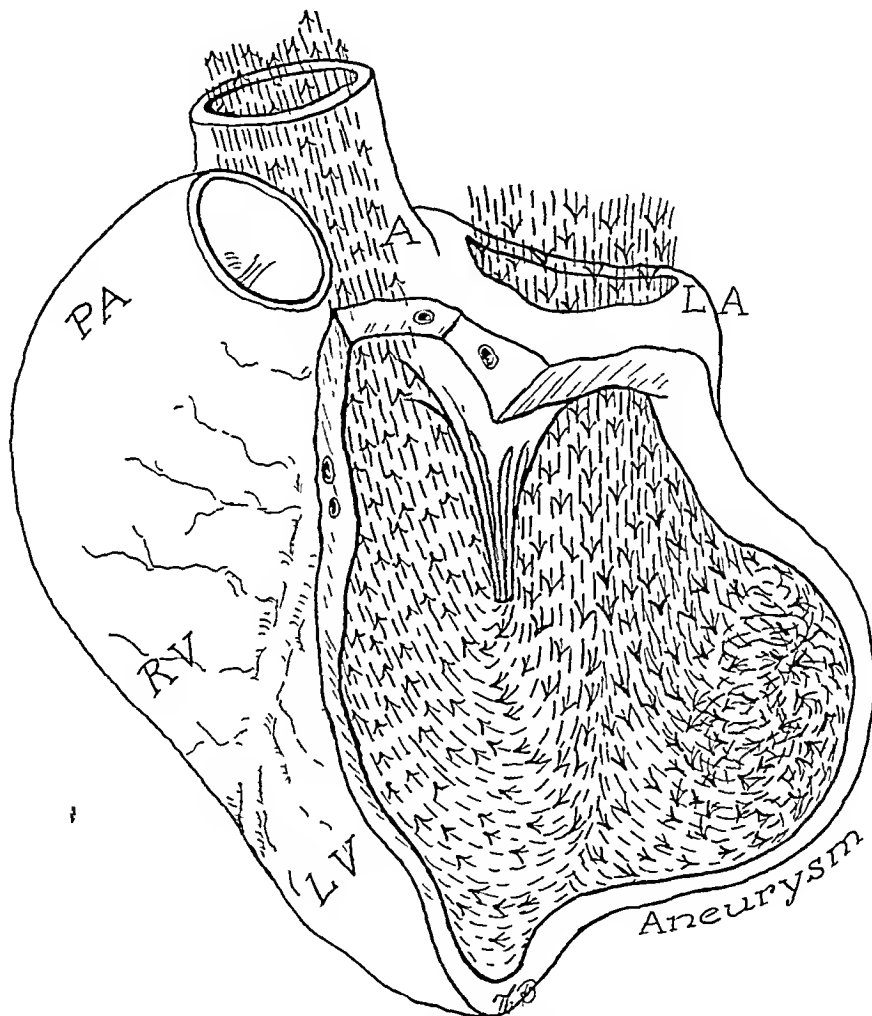


FIG. 1—Hemodynamics in presence of aneurysm Blood escapes into the aneurysm during systole instead of being expelled into the aorta

and which has some significance What I have in mind is the deliberate production of a cicatrix to support a dilating heart and also to prevent rupture of an aneurysm of the heart Experimentally, Holman and I<sup>7</sup> showed that the pericardium exerted a constrictive action against acute dilatation produced by plethora Whether a dilating heart can be helped by a supporting cicatrix on the outside of the heart is a question that cannot be answered It deserves investigation on patients The idea of placing a supporting graft over the aneurysm has obvious merits In the first place, a graft can be expected to

prevent rupture of an aneurysm. In the second place, an improvement in the circulation can be expected by reducing the size of the aneurysm. In the presence of an aneurysm, the aneurysm fills out with blood with each systole. Instead of expelling the total content of the left ventricle into the aorta, part of the content escapes into the aneurysm. This is indicated in Figure 1. It is not unlike a mitral valve leak.



FIG. 2—Roentgenogram of the chest showing aneurysm of the lateral aspect of the left ventricle. The excursion of the aneurysm during diastole and systole measured about 2 cm. The aneurysm bulged out as the ventricle contracted.

#### CASE REPORT

The patient, referred by Dr. Arthur Weihe, of Oak Park, Illinois, was a male, white, age 49. He was debilitated, and had the appearance of an old man. The patient gave a history of almost constant pain in the epigastrium. Eighteen months before admission he had an acute, severe attack of upper abdominal pain. The diagnosis of perforated gastric ulcer was made and celiotomy was performed. Two months later the patient had a second severe attack of pain in the epigastrium which radiated into the chest, left shoulder and down the left arm. The diagnosis of coronary artery disease was made. Treatment consisted of rest and administration of sedatives. Thereafter he was subject to recurring episodes of sharp anginal pain. Two months before admission to the hospital he suffered a particularly severe attack of pain. At that time a roentgenogram was taken and aneurysm of the left ventricle was demonstrated. He was referred for operation to prevent rupture of the aneurysm. A marked pulsation over

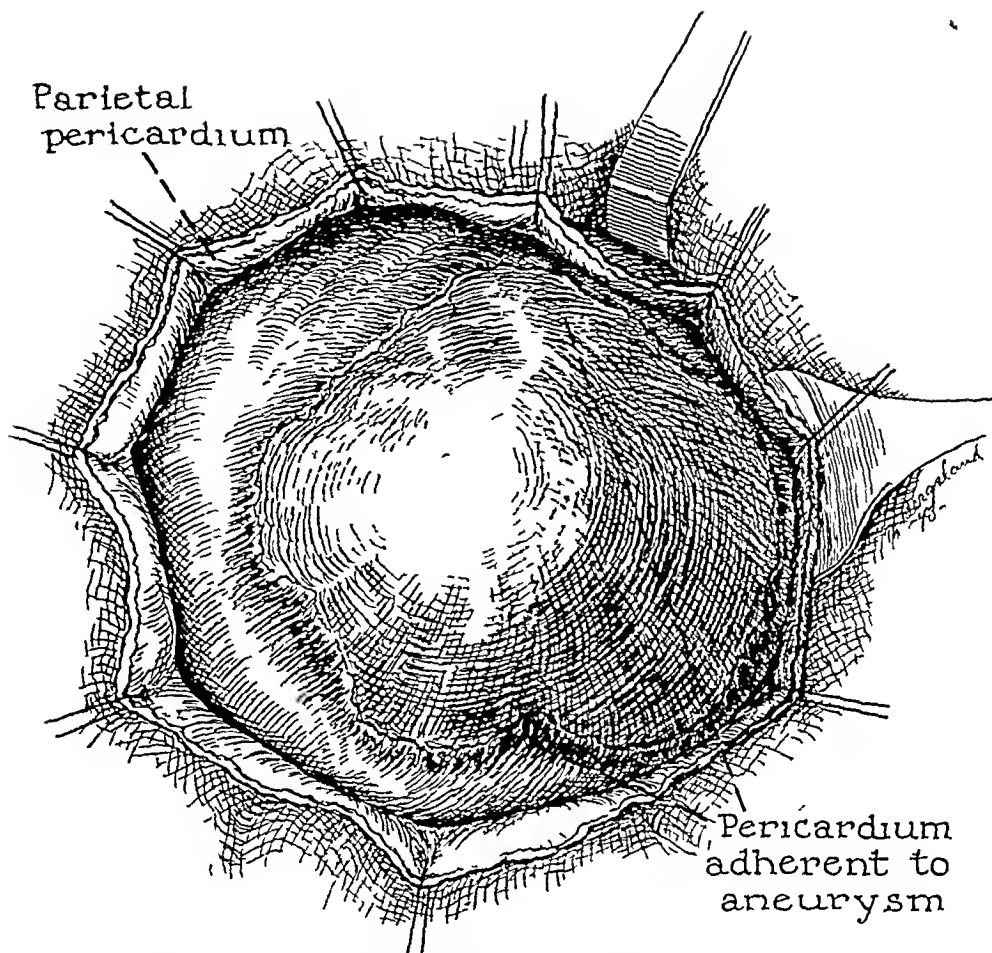


FIG 3—Parietal pericardium was adherent to the aneurysm. It was not separated from the heart. It was incised, leaving a patch adherent to the aneurysm.

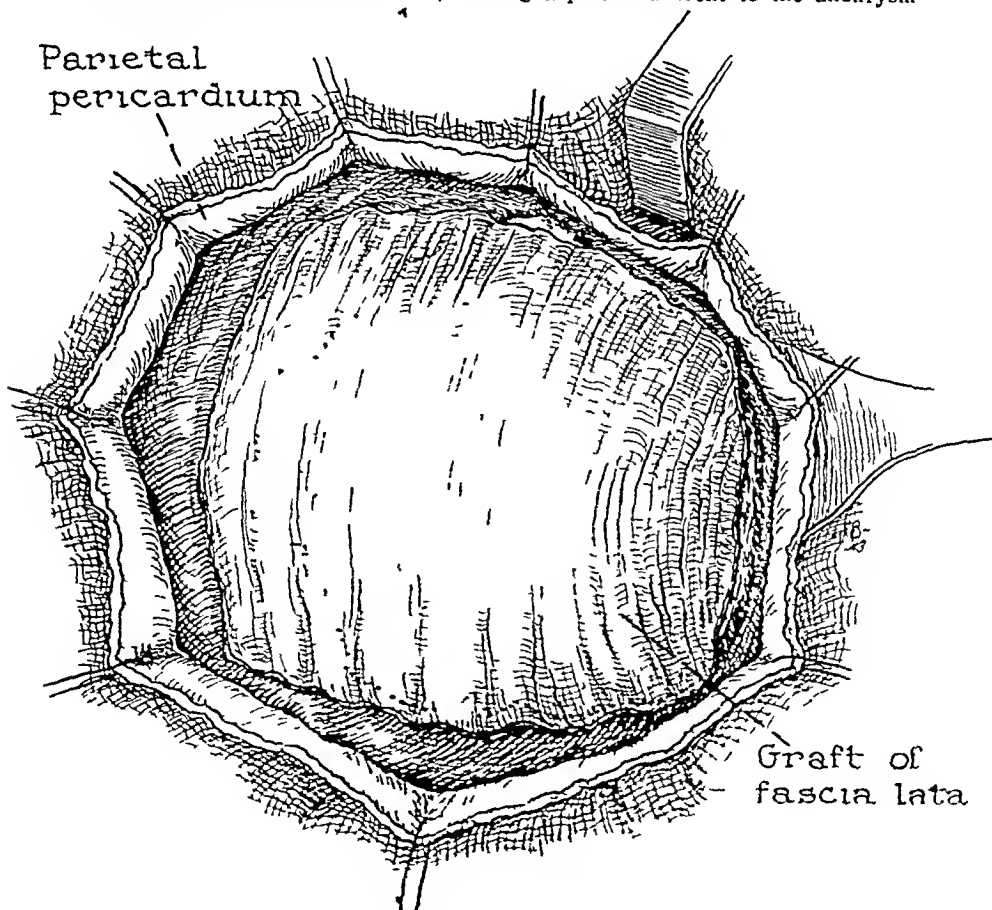


FIG 4—Graft of fascia lata placed over aneurysm. Dotted line indicates parietal pericardium adherent to aneurysm.

the precordium was observed. Fluoroscopic and film studies of the heart showed a large oval bulge, measuring  $4 \times 7$  cm, in the region of the lateral wall of the left ventricle (Fig 2). During cardiac systole this bulge became markedly distended. The aneurysm bulged out while the silhouette elsewhere became smaller. This pulsation was so marked that rupture appeared to be imminent. The electrocardiogram showed evidence of anterior and apical infarction. The sedimentation rate was normal, temperature normal, and white blood cell count normal. The patient was weak, he could not

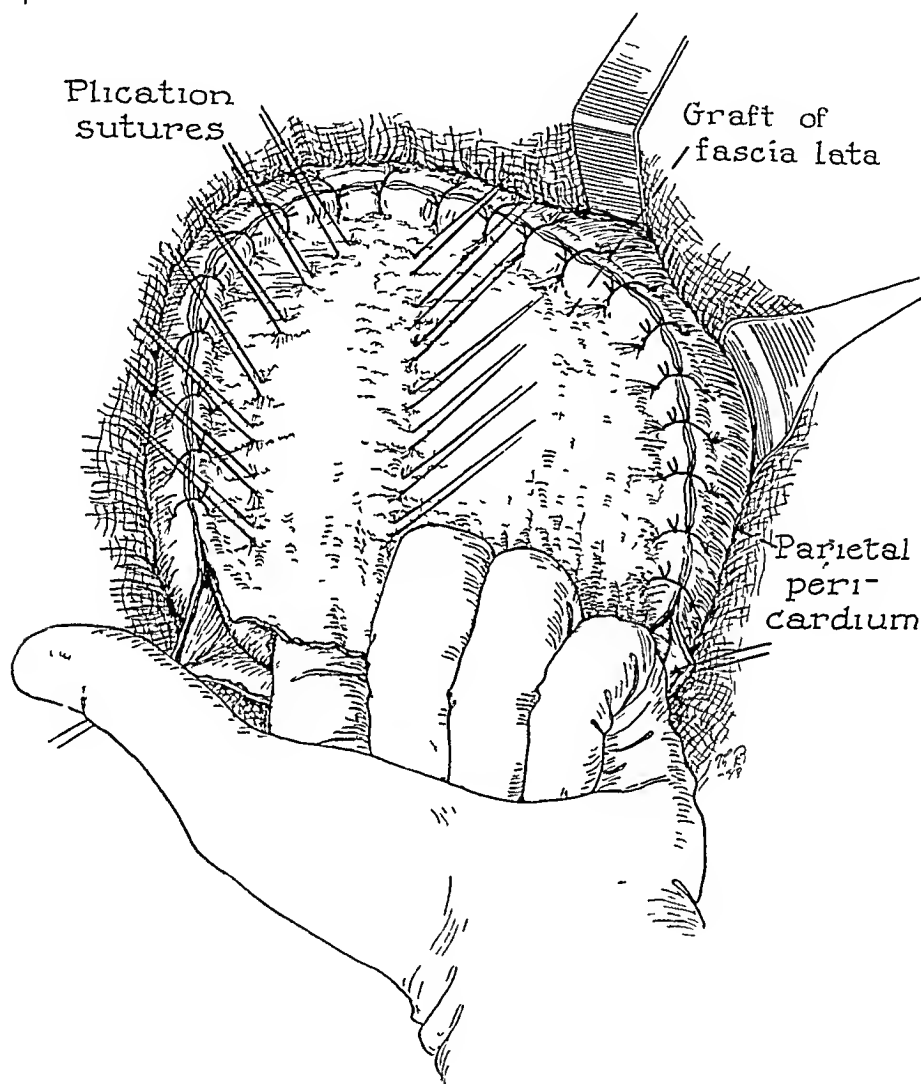


FIG. 5—Graft of fascia lata sutured to parietal pericardium. Finger inserted between graft and heart and two rows of sutures placed.

work, he was almost bedridden. Our blood pressure determinations were practically normal, but Doctor Weihe had obtained determinations of 94 Mm mercury, systolic.

*Operation*—June 12, 1942. The fifth and sixth costal cartilages and parts of the corresponding ribs were removed and the mediastinum was opened. The lungs were adherent to the mediastinal pleura, and these adhesions were gently separated. The pericardium was adherent to the aneurysm. It was incised around the base of the aneurysm in a circle about 8 to 10 cm in diameter (Fig 3). A definite increase in size of the aneurysm occurred after the pericardium was cut. The pericardium offered

## ANEURYSM OF HEART

support to the aneurysm. The aneurysm bulged out about 4 cm beyond the normal contour of the ventricle. The distention during systole was marked, and the possibility of rupture was present. Dakin's solution was applied by cotton pad to the surface of the aneurysm for a period of 11 minutes. A piece of fascia lata large enough to cover the aneurysm was cut and placed over the aneurysm (Fig 4). This graft was sutured by interrupted sutures to the parietal-pericardium (Fig 5). In order to furnish outside support to the aneurysm, a series of plication sutures were placed, as shown in Figure 6. These sutures when tied reduced the size of the graft and reduced the size of the aneurysm. Closure of the wound was carried out.

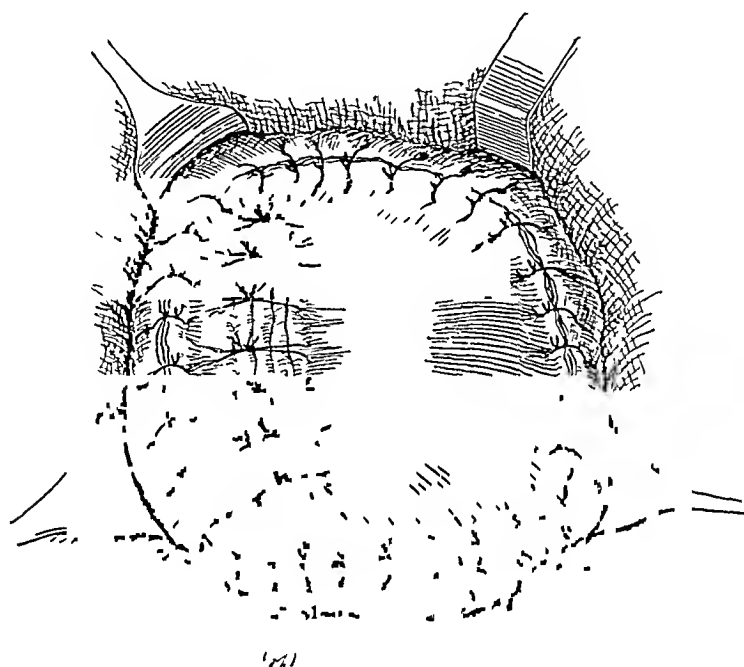


FIG 6—Plication sutures tied, and size of graft reduced. This afforded support to the aneurysm.

*Postoperative Course*—The patient developed fever and signs of pneumonia. A small amount of serous fluid was aspirated from the chest. The wound healed *per primam*. Two weeks after operation a few cubic centimeters of serous fluid were obtained from the wound. Within a few days the fluid increased in amount and became purulent. An intercostal catheter was inserted into the left pleural cavity and a liter of pus was obtained. Dakinization of the cavity was carried out. Cerebral manifestations of confusion and disorientation appeared. The patient died five weeks after operation.

*Postmortem Examination*—The fascial graft was everywhere adherent to the aneurysm. There was no evidence of infection in the graft. The graft of fascia lata was sealed to the pericardium and myocardium, and appeared as a firm cicatrix. On cross-section the graft of fascia lata and the adherent patch of pericardium appeared to be fused with the cicatrix of the aneurysmal wall. The latter was only a few millimeters in thickness. A mural thrombus, measuring 1.7 cm in its greatest thickness, was found in the aneurysm (Fig 7). There was no evidence that any of the thrombus had been swept into the brain. The myocardium was extensively degenerated into scar tissue. This cicatrix involved anteriolateral aspect of left ventricle and part of the interventricular septum. The descending ramus of the left coronary artery was completely occluded. The right coronary artery showed some changes but it and the circumflex ramus of the left coronary artery were patent. Other findings were the pleural empyema cavity which was drained, arteriosclerosis of aorta and cerebral arteries, and encephalomalacia of the cerebral cortex and thalamus.

In reference to application of this operative procedure for aneurysm of the heart, one can raise the question as to whether the attempt is worth while. In this patient the emaciation, the sclerotic changes in aorta and cerebral vessels, and the mural thrombus within the heart were factors that would make any operative procedure almost futile. In my opinion this operation



FIG 7—Cross section of heart. Note graft and silk sutures. The fascia lata and parietal pericardium are fused with the cicatrix of aneurysmal wall. The wall is extremely thin. Note thrombus in the ventricle.

would offer fair chance of success if it were performed upon a patient who did not show such extensive degenerative changes. The operation, in itself, is not a serious or drastic procedure.

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# INFECTED DISSECTING ANEURYSM OF THE ILIAC ARTERY FOLLOWING ARTERIOVENOUS FISTULA OF THE FEMORAL VESSELS\*

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HUNTER, in 1762, called attention to the dilatation of the proximal portion of the artery in his first case of arteriovenous aneurysm. Since that classical report dilatation of the artery to a varying extent has been reported frequently. From a study of the literature one might assume that its frequent mention would warrant the belief that dilatation of the artery entering an arteriovenous aneurysm is an essential part of the pathology. However, in a most painstaking study by Callender<sup>1</sup> of 447 reported cases of arteriovenous fistula dilatation was noted only in 57, or 12.7 per cent. Undoubtedly it was present but not noted in other reported cases but its constancy in arteriovenous aneurysm cannot be taken for granted. The late Mont Reid, a great master in the field of arteriovenous aneurysm, believed that dilatation of the artery occurred only after the lapse of years.<sup>2</sup> This was true in his experimental animals. Of the six clinical cases which he reported dilatation was seen only in those of long duration.

According to Holman's view,<sup>3</sup> based largely on extensive experimentation, proximal dilatation of the artery is to be explained on purely physiologic grounds. It is dependent primarily on an increase in the total volume of the circulating blood and more particularly on an increase in blood flow through the fistulous zone. This increase is one of the compensatory changes necessary to rectify the fall in blood pressure incident to the greatly decreased peripheral resistance in the presence of a fistula. This theory implies dilatation of the artery in all instances of arteriovenous aneurysm, at any rate in all instances of long duration, and this does not appear to be the case.

Regardless of the incidence of, and the theory to account for, proximal dilatation of the artery, extraordinary dilatation of the artery entering the aneurysm is rare. This communication is concerned with such dilatations and their significance. It therefore is appropriate to refer to the reported cases. In Callender's list are four cases, all from an early period, and all fatal. The first is Beaumont's,<sup>4</sup> in which the superficial femoral artery was greatly dilated admitting two fingers. The common femoral and external iliac arteries throughout their course were equally dilated, somewhat thinned, but otherwise healthy. In Fitzgerald's<sup>5</sup> case, reported in 1878, the popliteal artery above the arteriovenous aneurysm was somewhat dilated, the femoral artery was greatly dilated, but the external and common iliac were much

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more so, having a circumference three times that of the opposite side. The dilatation terminated abruptly at the upper end of the common iliac artery in a thin-walled prominent sacculus. The elongation and tortuosity of the dilated arteries were as prominent as the dilatation. The third case was reported by O'Grady<sup>6</sup>. There was a remarkable dilatation of the external iliac artery, which approached the abdominal aorta in size. Resembling a sausage, it was distended and tortuous, suggesting a coil of small intestine. Lucas-Championnière's<sup>7</sup> case, also, was one of remarkable dilatation of the femoral and iliac arteries.



FIG. 1.—Case 1. Roentgenogram showing the enlargement of the cardiac shadow.

It is impossible to ascertain what role was played by the marked or extreme dilatation of the arteries in the reported cases. Indeed, no particular clinical significance appears to have been ascribed to any degree of dilatation of the proximal artery, despite the fact that thinning of the wall is as characteristic as tortuosity and dilatation of the vessel. Although there are undoubtedly other reported instances, I have found only one case report in which the artery was described as presenting a problem at the time of operation. Reid and McGuire<sup>8</sup> report a case in which the femoral artery just proximal to the arteriovenous aneurysm "was the largest artery Reid had ever ligated," more than one inch in diameter. Its wall was so thin that blood actually oozed through it proximally when the ligature of tape was tied. The bleeding stopped under gentle pressure with gauze.

The possible problem arising out of the more severe forms of dilatation is to be seen in the case herewith reported (Case 1), which is not intended to detail all the features of interest

**Case 1**—Mt Sinai Hospital No 490586 I H S, age 58, was admitted in mild heart failure of short duration, with a history of swelling of the left leg of three weeks' duration, and with an obvious popliteal arteriovenous aneurysm. The latter was the result of a stab wound sustained 40 years before. There were few if any symptoms referable either to the aneurysm or the cardiac status over this period of many years. The outstanding local feature, in addition to the usual evidence of popliteal arteriovenous aneurysm, was an enormous tortuous dilatation of the femoral artery throughout its course. This is illustrated in the diodrast visualization of the artery (Figs 1 and 2). There also is to be noted diffuse calcification of the vessel (Fig 3). The cardiac lesion appeared to be a combination of mitral stenosis and insufficiency (Fig 4). Because of fever which was present without obvious cause, a blood culture was taken, which revealed diphtheroid bacilli.

The possibility of the aneurysm as the source of the bacteremia was entertained, particularly in view of the extraordinary case reported recently from our surgical service by Touroff<sup>9</sup>. It was also thought that the cure of the aneurysm might improve the cardiac status as it has in other cases. Accordingly, an obliterative endoaneurysmorrhaphy was performed. The interior of the sac disclosed no vegetations. The operation was uneventful.

The postoperative course was uninfluenced both as regards the bacteremia and the size of the heart. There was no recurrence of the aneurysm. The possibility remained that the enormously dilated femoral artery might contain vegetations from which the bacteremia was derived, and act as the aneurysm might have done to produce heart failure. Three weeks after aneurysmorrhaphy the femoral artery was excised under local anesthesia. The interior of the artery disclosed no vegetations and it was, therefore, assumed that a vegetative *endocarditis* was the source of the bacteremia.

The postoperative course again appeared to be uninfluenced by operation. Death occurred suddenly a week after operation, apparently the result of a cerebral vascular accident. The features of the autopsy (P M No 12247) of special interest were

Hypertrophy and dilatation of all chambers of the heart, subacute bacterial endocarditis involving the aortic valve (from which the same diphtheroid organism was



Fig 2—Case 1. Roentgenogram showing the calcification in the wall of the greatly dilated femoral artery.

grown as in the blood stream), and dilatation of the iliac artery on the affected side (as well as some general dilatation of the aorta)

The case of infected dissecting aneurysm (or infected hematoma in aneurysmal dilatation) of the iliac artery following arteriovenous fistula of the femoral vessels, is as follows

**Case 2**—Mt Sinai Hospital No 502552 W L, a physician, age 48, was admitted, March 8, 1943, with the history of a bullet wound in the lower left thigh sustained when eight years old. Thereafter, there was always some slight swelling of the left leg

FIG 3



FIG 4



FIG 3—Case 1. Roentgenogram following injection of diodrast into the femoral artery. Tortuosity and dilatation of the femoral and popliteal arteries are pronounced.

FIG 4—Case 1. Roentgenograms taken immediately after that shown in Figure 3. The saccular dilatations between artery and vein and the dilatation of the popliteal vein are revealed.

Throughout many years he was entirely symptom-free, and engaged in active practice. Excessive pulsation in the left inguinal region and thigh had always been noted. Apparently the only symptom that led to an operation upon the arteriovenous fistula, in 1934, was an episode of pain in the posterior aspect of the thigh (in 1933). Operation was performed by J deJ Pemberton of the Mayo Clinic, in 1934, who kindly provided data which are abstracted as follows

Enlargement of left leg with distention of the superficial veins Thrill and bruit over the arteriovenous fistula, cardiac hypertrophy Blood pressure 120/60 Operation consisted of excision of a segment of the left femoral artery and vein, which included the arteriovenous fistula (opening about 1 cm in diameter)

The arteriovenous aneurysm was cured, and there is not the slightest trace of any recurrence Apparently it was assumed that the pulsating mass in the inguinal region would recede, but it remained unchanged In recent years there were occasional cramps in the left calf on brisk walking There have been no other symptoms

Five days before admission dull ache in the left inguinal region began, with feverishness and anorexia The aching pain increased gradually in intensity The day before admission there was a five-minute chill

On admission, the cardiac and general physical examination revealed no abnormalities Approximately normal cardiac contours were noted in the chest films The incisional scar at the site of repair of the arteriovenous aneurysm was free from any pulsation, and established that the aneurysm was cured In the left inguinal and iliac region was a prominent, sausage-like pulsating mass with redness of the overlying skin (no local medication had been applied) Forcible pulsation was visible and palpable The area of aneurysmal dilatation, which obviously involved the iliac artery, appeared to extend upwards to involve the whole length of that vessel (including the common iliac?) The left leg was larger than the right, with superficial veins somewhat engorged In the upper thigh the circumference on the right side was 50 cm, on the left, 54.5 cm At the lower thigh, the right measured 40, the left 43 cm

The study of the circulatory dynamics was made by Dr W M Hitzig With an initial venous pressure of 6 cm there was no rise on compression of the right upper quadrant The circulation time of "arm-to-tongue" (decholin) was 11 seconds Thus, the cardiovascular dynamics were normal

The diagnosis and decision as to procedure were arrived at after a short period of observation There was persistent pain in the thigh and leg, and persistent warmth and redness over the inguinal mass On the day of admission there was a five-minute chill with slight rise in temperature, but the next day a fifteen-minute chill occurred, with temperature of 104.6° F A blood culture was negative, Wassermann negative

Operation was performed on the second day after admission, with the diagnosis of an infective lesion within the greatly dilated iliac artery A liberal extraperitoneal approach exposed the mass from the bifurcation of the aorta to the inguinal ligament The lower portion of the incision was extended to the thigh in order to expose the upper portion of the femoral artery The peritoneum was exposed and stripped away to the midline The cellular tissue overlying the mass was acutely inflamed, edematous, and adherent The mass was a pulsating, enormously dilated external and common iliac artery It extended upwards to within 3 or 4 cm of the bifurcation of the aorta, where it narrowed abruptly to the normal size of the common iliac artery Similarly, at the lower end the mass narrowed down to an apparently obliterated femoral artery just below Poupart's ligament The shape and size of the mass are best seen in Figure 5 On palpation, the sausage-like mass appeared to transmit pulsation although some measure of through pulsation could not be excluded Only towards the end of the dissection was the iliac vein identified as a thick-walled, collapsed, tape-like structure adherent to the deep surface of the dilated artery

The aneurysmally-dilated artery was removed completely Under good visualization the vessel was exposed a short distance below the bifurcation of the aorta It was severed between stout silk ligatures at the point of narrowing immediately above the dilated sac The release of the sac was carried out from above downwards by sharp and blunt dissection through a good plane of cleavage from an encasing inflammatory connective tissue layer No significant vessel was encountered until the inguinal ligament was approached A large arterial trunk, which may have been the internal iliac artery,

was there encountered and was severed between ligatures. The release was continued a short distance on the thigh below the termination of the mass, at which level the old operative field was entered. There appeared to be complete obliteration at the point of severance of the femoral artery. The wound was closed in layers.

The specimen proved to be a dissecting aneurysm of the iliac artery. It was 16 cm long, with a circumference of 15 cm at its widest proximal portion, and an average of 11 cm over the distal portion. The sac terminated below in the completely

FIG 5

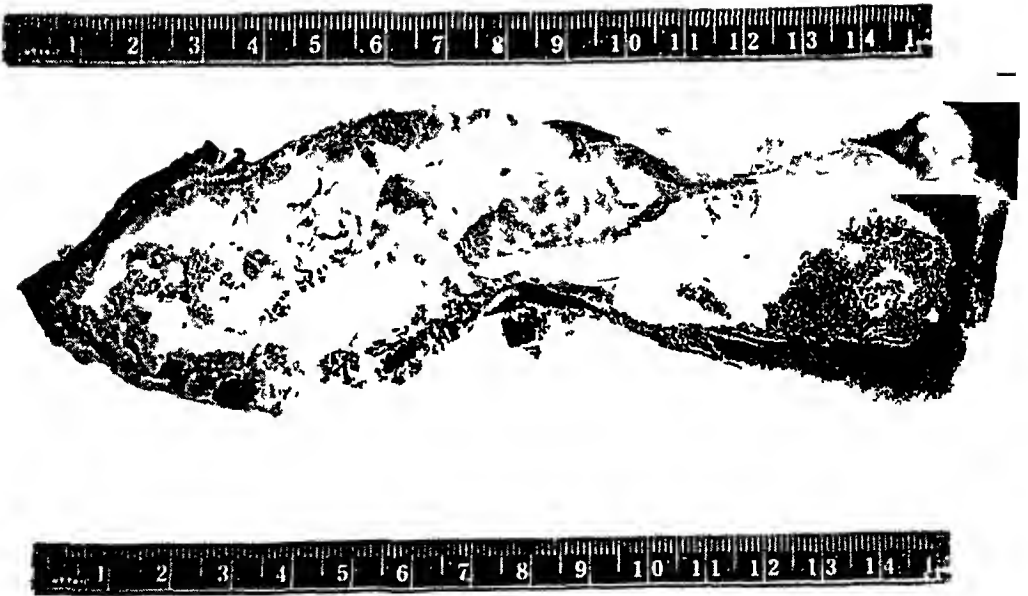
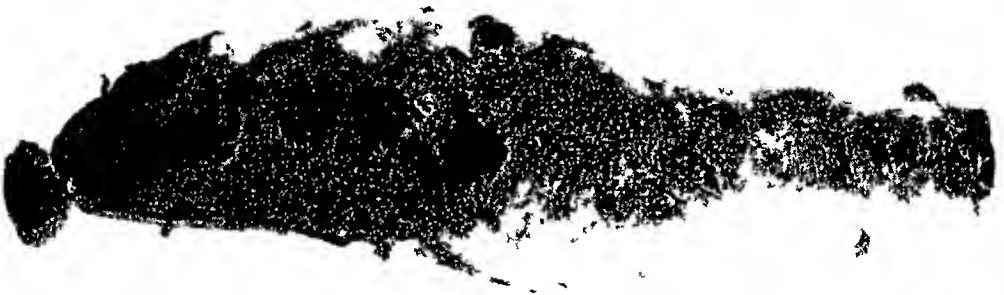


FIG 6

FIG 5—Case 2. Photograph of the excised aneurysm of the iliac artery.  
FIG 6—Case 2. Photograph of the specimen opened, showing a dissecting aneurysm, with an adherent, infected blood clot.

obliterated femoral artery with a grayish-white homogeneous tissue laid down in concentric layers. The lumen was occupied by blood clot. In the proximal portion the thrombus was pinkish-gray, adherent, and partly organized. A partial lumen could

be identified. In the distal 7 cm there was complete occlusion, chiefly by adherent grayish material. Part of this old, obviously infected clot was semisolid and free. The intima, to which the blood clot was for the most part loosely adherent, was continuous in one area and in another area (as seen in Figure 6) was detached by the blood which has dissected beneath it. Calcification could be felt beneath the intima. The wall of the artery measured between 2 and 3 millimeters.

The microscopic examination revealed thinning, atrophy, and arteriosclerosis of the wall of the artery, with infected thrombus containing gram-positive cocci (culture taken at the time of operation was reported enterococcus). The microscopic examination of the adjacent vein confirmed the impression derived from gross examination, namely, phlebosclerosis with complete obliteration of the lumen by fibrosed thrombus.

The postoperative course was uneventful. The temperature reached normal levels by the third day and remained so thereafter. There was increased warmth over the left leg for a period of about ten days, presumably due to the severance of sympathetic fibers. The blood pressure remained unchanged. The wound healed *per primam*. The patient left the hospital about three weeks after operation. There was some weakness in the left leg for several weeks thereafter. There has been no appreciable edema, and there is now (one year after operation) no difference in size between the two legs. The patient remains quite symptom-free.

**DISCUSSION**—These two cases provide a commentary on some of the statements which have been made concerning dilatation of the artery proximal to the aneurysm. In both instances the traumatic aneurysms date to childhood, and thus offer support to the view that extreme dilatations probably depend on the duration of the lesion rather than the size of the arteriovenous fistula. In neither case can the enormous proximal dilatation be said to have contributed to the heart failure. The first patient was symptom-free throughout the many years in which he carried both the aneurysm and the dilated femoral artery. The second patient presented the characteristic reduction in the size of the heart after the operative cure of the aneurysm. The heart remained of normal size despite the presence of the ectatic iliac artery over a long period of time. On the other hand it is noteworthy that the dilatation did not recede, as might have been anticipated, after the cure of the aneurysm had been achieved. No clinical significance can, therefore, be attached to the mere presence of the extreme dilatation of the proximal artery in these two cases.

In the first case, operation was performed primarily because of the possible source of bacteremia from vegetations within the aneurysm or the dilated proximal artery. This proved to be incorrect, for the source was found to be within the heart. However, the same assumption might prove to be correct in another case. In the second case, the source of infection was the infected thrombus within the dilated iliac artery. Although the blood culture was negative, the chills and fever before operation not only indicated a patent blood stream communicating with the aneurysm but also the likelihood of a positive culture if operation had not intervened.

Concerning the possible usefulness in circulatory dynamics of the dilated proximal artery these two cases appear to demonstrate that, insofar as extreme dilatations are concerned, no desirable feature can be ascertained. The

dilated atrophic channels appear to be nothing more than blood sewers calling for additional cardiac effort to push their contents along. On theoretic grounds, it can be said that their elimination should improve cardiovascular dynamics. On the basis of the reported case it can be said that their presence comprises a menace.

#### CONCLUSION

Severe grades of dilatation of the proximal artery in cases of arteriovenous aneurysm of the popliteal or femoral vessels should be treated by excision of the dilated artery. In the presence of infection within the ectatic artery excision is imperative.

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# LIGATION OF THE ABDOMINAL AORTA

## CASE REPORT

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THIS CASE seems worth reporting because of the small number of aortic ligations on record.

**Case Report**—The patient was a man, age 61. There was nothing of interest in his past history, except an attack of vertigo four and one-half years before, followed by deafness.

He was first seen at this hospital, December 2, 1942, complaining of severe epigastric pain which had come on suddenly two days before, and had been present without respite ever since. There was no history of any previous gastro-intestinal symptoms and no radiation of pain.

Physical examination showed a well-nourished man in evident pain. No important abnormalities were evident except in the abdomen. The heart showed no murmurs, and the rate and rhythm were regular. Blood pressure 140/90. There was no abdominal rigidity, but there was marked epigastric tenderness, and a mass, which was thought to pulsate in an expansile manner, was felt below and somewhat to the left of the umbilicus. All deep reflexes seemed normal.

Urine: Sp. gr. 1.018, no albumin or sugar, and no red blood cells or pus. Blood showed hemoglobin determination of 13.1 Gm. per 100 cc. blood, red blood cells 4,200,000, leukocytes 6,150. Kline exclusion test for syphilis was negative.

Electrocardiogram, December 17, 1942, showed large Q waves in leads II and III, with elevated ST segments in leads II and III, and deeply inverted T waves in leads II and III. Precordial lead CF V showed depression of the ST segment. The changes were believed to be typically those of an acute posterior myocardial infarction. In addition, a tentative diagnosis of abdominal aortic aneurysm was made.

He remained in the hospital 21 days. During this time his blood pressure remained about where it was on admission. He was discharged on December 26, 1942, and returned for observation on January 30, and February 20, 1943. He seemed to be doing well. His blood pressure had risen to about 170/110.

On March 3, 1943, following unwise exertion, he had severe abdominal pain, collapsed, and was brought to the hospital the next day. He had diarrhea, urinary frequency, low abdominal pain, and his blood pressure was 50/?.

Below the umbilicus, and to the left, a pulsating mass was noted about the size of a large orange, there was no bruit. His pain ceased, and his blood pressure rose to 110/70 on March 5. His urine showed red blood cells, albumin and granular casts.

On March 6 there was another episode of lower abdominal pain, and his hemoglobin was found to be 7.9 Gm. per 100 cc. blood. The patient seemed to be in shock.

On March 7 the condition remained about the same. The hemoglobin was 6.2 Gm. per 100 cc. blood, and the mass had increased in size, filling the left side of the lower abdomen and extending along the flank.

The possibility of a ruptured ectopic kidney was suggested, though the diagnosis thought to be more probable was rupture of an abdominal aneurysm.

The patient's condition was desperate and it seemed best, in view of the possibility,



slight as it was, of there being a ruptured kidney, to give him the benefit of the doubt and explore the abdominal tumor. At this time his blood pressure was 105/70, and the hemoglobin was read at 6.2 Gm per 100 cc blood. He was prepared by giving a transfusion of about a pint of blood. When taken to the operating room, his blood pressure was 110/70. Arrangements were made to start another transfusion at the beginning of the operation. The patient was laid slightly on the right side with the left side supported by pads, raising it a few inches from the table.

*Operation*—Under ethylene gas, an incision was made similar to the continuation of the ordinary incision for exposing a kidney, and ran from near the tip of the twelfth rib down into the inguinal region. The fibers of the external oblique muscles were separated, and those of the internal oblique and transversalis cut across. A great mass of clotted blood was found and evacuated. The viscera were pushed upward and what was evidently a ruptured aneurysm exposed. Up to this point there had been no fresh bleeding, but it now started again. Quickly, using the index finger, the aorta above the aneurysm was dissected, encircled, grasped and compressed, completely controlling the bleeding. There was found to be a rather long tear in the anterior surface of the aneurysmal sac, which contained blood clot, and two openings, which were supposed to be the rough sclerotic orifices of the common iliacs, could be palpated. After due consideration, there seemed no alternative other than to ligate the aorta, which was done with two layers of ribbon gut. Two cigarette drains were then inserted to the region of the aneurysm and the wound rapidly repaired. The duration of the operation was a little less than one hour, during which time the patient received another pint of blood by transfusion. His condition at the end of the operation was about the same as at the beginning. No pulsations could be felt in any of the arteries of the leg.

*Postoperative Course*—That evening, two hours postoperative, his blood pressure was 148/76, pulse 150.

The following morning his blood pressure was 140/70, pulse 110, and the patient recognized his attendants. His legs were cool, but not cold, nor discolored, but he did not move them, and there was no pulsation in any arteries.

Suddenly, at 11:45 A.M., he developed Cheyne-Stokes' respirations, his pulse and blood pressure became imperceptible, and he died 20 minutes later. There was no sign of hemorrhage along the drains.

Unfortunately, his sister (his only relative), though she was a trained nurse, would not give permission for an autopsy, in spite of many efforts made to persuade her.

**COMMENT** We should like to have learned the exact cause of death, which may have been pulmonary embolism or coronary thrombosis. We did not think it was due to fresh hemorrhages from the aneurysm. We should also have liked to have observed the site of the ligation, for it would have been better judgment to have used cotton tape instead of an absorbable ligature for such a large vessel.

In 1940, Elkin reported on all cases of ligation of the aorta reported up to that time. He found 13 instances of complete ligation. Only one of the patients survived the operation. Five lived 24 hours or longer, one, 65 hours. Our patient survived the operation 18 hours.

Matas reported a patient who survived ligation one year and five months, dying then from tuberculosis, but this was not a complete ligation, for the aorta was found to be patent at autopsy.

Brooks reported a patient who survived ligation for three months, dying then of intestinal obstruction. He had returned to his work as a truck driver.

in the interim, apparently without any impairment of circulation below the ligature. In this case, however, the aneurysm, of luetic origin, was very large and of long duration, and there had been development of collateral circulation previous to the ligation.

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# SURGICAL ASPECTS OF PANCREATIC FISTULA\*

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THE EVER WIDENING SCOPE of abdominal surgery has encompassed within the past twenty years the intriguing and difficult operative procedures upon the pancreas. A common sequela of such operations has been the advertent or inadvertent creation of a pancreatic fistula associated with the host of problems attendant upon such a result. Opportunities to study and record the effects of the continued loss of pancreatic fluid upon the human have been rare although the problem has been given detailed attention in the experimental animal. It has been our privilege to have under observation for varying periods of time three patients with pancreatic fistulae of varying degrees of severity, one of which was producing as much as 1,700 cc of pancreatic juice a day. This amount is in great contrast to the quantity of pancreatic juice lost in many of the cases reported in the literature, where the average ranges from 250 to 500 cc in 24 hours.

An unusual privilege was afforded to make observations in one of these cases. The amount of pancreatic fluid secreted was large enough so that conclusions regarding the various aspects of flow were of great value. Opportunity was thus afforded to study

- 1 The results of the continued loss of pancreatic fluid upon plasma electrolytes

- 2 Replacement therapy to correct deficiencies produced in the plasma electrolyte pattern resulting from the loss of pancreatic fluid

- 3 Drugs available to slow the flow of pancreatic juice

- 4 The creation of a mechanical device to prevent irritation of the skin from pancreatic juice

For purposes of orientation it might be well to add here, parenthetically, that a number of causes may produce a pancreatic fistula. Probably the most common etiologic factor is drainage of a pancreatic cyst, as marsupialization is the usual procedure in the surgical treatment of this condition. A fistula may follow operation for acute inflammatory conditions or, in not so rare instances nowadays, may be the result of a stab or gunshot wound of the abdomen. Operative injury to the pancreas with the creation of a fistula may follow surgery either upon that particular organ or upon one of the adjacent structures.

As far as treatment of such fistulae is concerned, it is our feeling that all such fistulae cannot be treated in the same manner. Even as other specific surgical conditions these demand individual variations in therapy. We are certain that the patient should be restored to a metabolic normal before the

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idea of surgery is entertained. Then, an additional period of observation is indicated to permit spontaneous closure. If, after a reasonable period, such a closure does not occur, surgical intervention is justified. The three case reports which follow exemplify this concept.

One patient from this small group is illustrative of the most severe type of change in electrolyte and nutritional balance which may be seen resulting from any abdominal fistula. He is a 25-year-old white male, who sustained a severe perforating wound of the abdomen from a shell fragment. Details of the immediate care are lacking, but the patient does mention receiving 250 cc of plasma preoperatively. Available records indicate that when celiotomy was performed on the day of injury a small stellate laceration of the upper surface of the liver, perforation of the gallbladder, laceration of the stomach and a retroduodenal hematoma were found. Although specific mention of pancreatic damage was not made on the brief operative note, injury was present, as proven by the subsequent development of an external pancreatic fistula. The various injuries were sutured, although the hepatic laceration was not disturbed, as a hemorrhage from it was not seen. His postoperative course was somewhat stormy. Effective supportive treatment in the form of suction siphonage and sodium sulfathiazole intravenously, combined with excellent surgical care, carried this individual through a rather dangerous period.

The first mention of a pancreatic fistula was made on the 13th postoperative day. Five days later a catheter was inserted into the tract and negative pressure by means of a water-suction device applied. Subsequently, considerable maceration of the skin surrounding the site of drainage was noted.

Laboratory data obtained at this time were of more than usual interest. A moderate degree of anemia was associated with a somewhat severe leukocytosis. Collection and examination of the fluid draining from the fistula proved that it was of pancreatic origin. The diastase value of this fluid was reported to be extremely high, 160,000 units per cc. It contained a small amount of trypsin, and its  $p_{\text{H}}$  range was from 7.5 to 8.0. The value for blood diastase was 320 units per cc, while that of the urine was 1,600 units per cc. Analysis of the stool for fat content revealed a relatively normal value of about 24 per cent.

His general condition was considered satisfactory enough to justify celiotomy for correction of the fistula, which was performed about one month after injury. Entrance into the peritoneal cavity was gained through a left upper rectus incision, with retraction of the muscle. The fistula was isolated, the dissection carried down through the gastrocolic omentum to the head of the pancreas, and the metallic foreign body which had produced the injury was located between the aorta and the duodenum. Adhesions in this area were marked, so that after due reflection upon the technical difficulties presented, the origin of the fistula was simply closed, the tract resected, closure of the abdominal wall and insertions of drains were performed in the customary

manner. However, drainage of pancreatic fluid was again noted soon after operation.

Notwithstanding this, improvement took place, and subsequently he was considered in a satisfactory condition to be evacuated to a Base Hospital in the United States. Upon admission to this hospital, a little less than four months after injury, the patient was found to be in a dehydrated, emaciated state, having lost 45 pounds in weight. The slightest exertion brought on undue dyspnea and fatigue. Anorexia was marked, and even the most tempting food failed to arouse his appetite. Lethargy and lack of interest in his environment was profound. Examination revealed little save what has been previously mentioned. A pancreatic fistula was found in a partially healed paramedian incision in the left upper quadrant. Studies of the individual blood constituents, made shortly after admission, revealed that marked deviations from normal were present. The hematocrit on initial examination was found to be 44 per cent, a relatively normal determination if it were not for the fact that this individual was markedly dehydrated, and had suffered a great change in his fluid balance. Plasma sodium was found to be 113.3 milli-equivalents in marked contrast to a normal value of 142 milli-equivalents, and emphasizes the rather serious loss of base which had occurred. Marked diminution of the plasma chlorides was also present, the plasma chloride value being 91.2 compared to the normal of 103 milli-equivalents. The total serum protein was 7.96 Gm per cent, of which 4.92 Gm were albumin and 3.04 Gm were globulin. (Normal serum protein is 7.0 Gm per liter.)

Loss of pancreatic fluid varied from about 1,000 to 1,770 cc in 24 hours. The flow was found to be quite continuous, and the predominant basic ion, sodium, was present in an amount almost approximating the quantity found in plasma itself. The bicarbonate ion was a major constituent of the cations in the fluid.

The pancreatic juice collected through this external fistula contained a considerable concentration of calcium, which would, in the absence of the fistula, have been secreted into the upper intestinal tract. This we feel is a previously unrecognized fact in calcium metabolism. Examination of a pooled specimen revealed a concentration of 2.2 mg per cent. This figure is more significant if one recalls that the value of the diffusible calcium of the plasma is about 5.5 mg per cent. In this particular instance 40 per cent of the total diffusible calcium of the blood plasma was being lost. Bone demineralization was not found by roentgenologic examination.

We were gradually led into making a series of physiologic observations while pursuing corrective surgical therapy. These will be reported in detail elsewhere. Obviously, the patient was not in condition at, or shortly after, the time of admission for operative treatment, and he was, therefore, prepared for eventual surgical correction of the fistula. As a matter of record the fistula closed spontaneously, and this fact is of major importance. Spontaneous closure occurred at a time when we considered the patient to have reached maximum preoperative improvement. At this time, concentration

of the various plasma electrolytes was within normal limits and the patient was in a positive nitrogen balance, having gained about 30 pounds in weight. However, to revert to the sequence of circumstances attendant upon admission, it should be noted that the fistula was producing fluid in such quantities that although spontaneous closure was considered, it was thought not quite possible. This episode, again, substantiates the fact that wounds of any sort are more prone to heal if normal physiologic and metabolic conditions are restored.

The patient was placed on a high protein, high caloric diet, but during his early days of hospitalization he had but little appetite and, at times, even refused fluids. Solutions of physiologic saline and glucose were administered intravenously when fluid intake dropped below estimated requirements. After several days of care his appetite returned. Food in relatively large amounts was easily taken, and a fairly rapid gain in weight ensued. Five weeks after admission, the plasma electrolyte pattern had assumed a relatively normal form. Evidence of a moderate degree of anemia was still present, as the red cell count was 3,500,000 per cc, and the hemoglobin content 10.2 Gm/100 cc. One thousand cubic centimeters of citrated whole blood was administered to the patient at this time. Subsequent determinations revealed that the number of erythrocytes had risen to 4,310,000 per cc, and the hemoglobin to 13.8 Gm/100 cc.

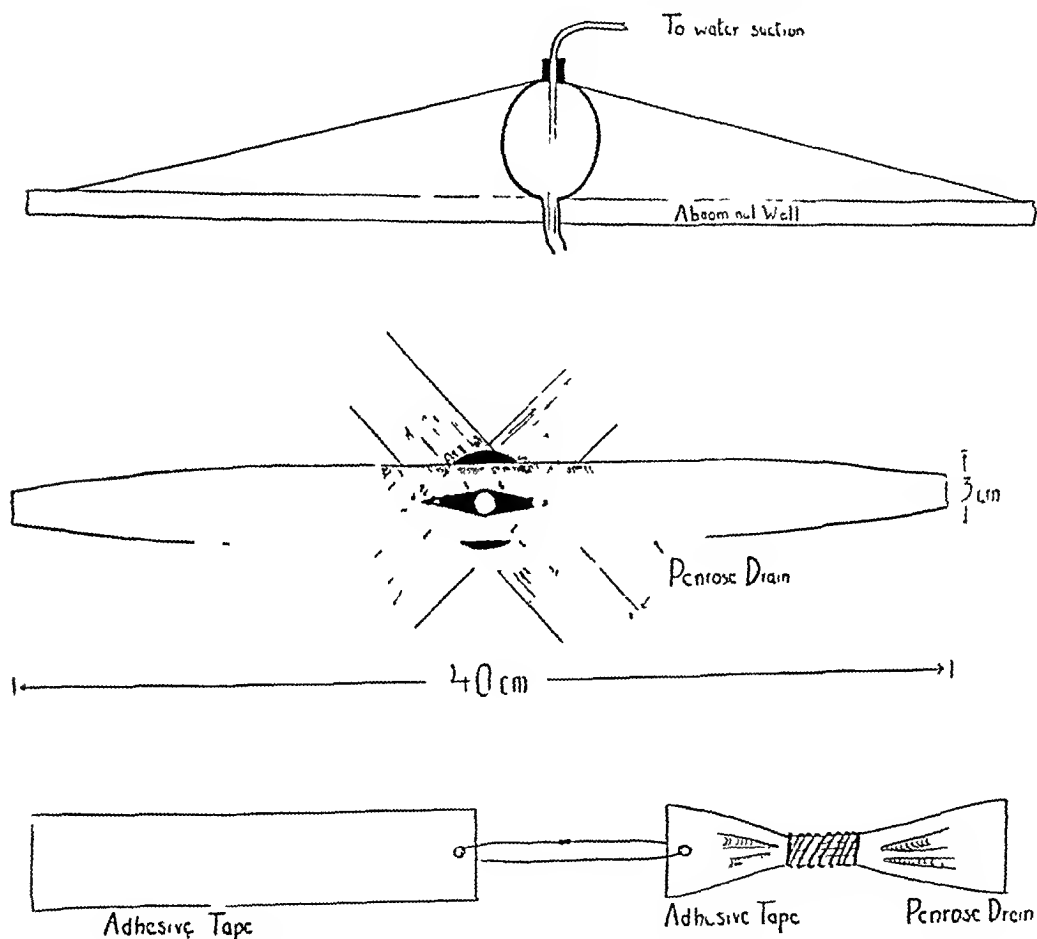
The collection of pancreatic juice from the fistula proved an exasperating problem during the early days. In addition to a desire to collect the fluid for oral administration, the surrounding skin had to be protected. A third consideration was the wish to have a method of collection which was complete, in order that some conclusions regarding volume secretion might be drawn when various drugs were administered. Several forms of apparatus, all employing a catheter and some type of suction were tried, before a satisfactory mechanical device was made. We finally settled upon the following:

The rubber bulb of an Asepto syringe was perforated at the top and a No. 14 French urethral catheter was passed completely through it (Fig. 1). The rounded tip of the catheter was cut off and a second hole made in the catheter just at the point where it passed through the bulb. Three pieces of Penrose drain 40 cm long and 3 cm wide, were perforated longitudinally at their middle and placed over the projecting end of the bulb (Fig. 2). The ends of the drains were covered with adhesive and attached, as shown in Figure 3, to a second piece of adhesive tape or the familiar "Montgomery tape." A piece of roller bandage was placed between the two strips of adhesive, tightened to the necessary degree, and tied. The catheter was connected to a water suction with provision for maintaining a negative pressure of about 10 cm of water. This not only provided for removal of the accumulated pancreatic secretion but produced a negative pressure differential which tended to seal the bulb in place. The bulb was further stabilized in its position by the elastic bands described above (Fig. 4).

In addition a thin mixture of aluminum paste was used on the skin to advantage

Of the many drugs that were used to influence flow through the external fistula, three will be but briefly discussed at this time

- A Ephedrine proved an effective means of diminishing the amount of collected pancreatic juice
- B Epinephrine acted as expected, the effect being similar to ephedrine, although much more dramatic in rapidity of onset and diminution of flow
- C Atropine produced a marked decrease in pancreatic secretion



FIGS 1, 2, and 3—Showing the general construction of the collecting apparatus employed

Two other patients, who suffered from a pancreatic fistula, were also subjected to observation. One was a 24-year-old white male, who sustained an abdominal injury in an automobile accident. Persistent abdominal pain was present for about three weeks and, when he was later admitted to a hospital, a large tender mass was found in the epigastrium. Celiotomy was performed on the third day of his hospital stay, and marsupialization of a pancreatic cyst was accomplished. He was eventually submitted to our care with a history of drainage of about 500 cc of pancreatic fluid a day from the fistula created at operation.

Physical examination revealed normal findings, with the exception of

those in the abdomen. A fistulous opening was present in an otherwise healed left midrectus incision, and from it a colorless fluid drained.

The results of laboratory examinations at the time of admission showed R B C, 5 080,000, Hb 90 0 per cent, W B C 12,300, hematocrit 46 8 per cent, sed rate 0 60 Mm/min, N P N 24 8 mg per cent, serum protein 6 98 Gm per cent, serum albumin 4 50 Gm per cent, serum globulin 2 47 Gm per cent, chloride 96 0 m eq/L, carbon dioxide combining power 30 9 m eq/L, prothrombin time 26 0 secs.

Under hospital care, the quantity of pancreatic fluid lost through the external fistula gradually decreased and spontaneous closure occurred about five weeks after admission. It was felt here, that a waiting period, with the patient in an optimum metabolic state, was justified to permit nonoperative closure.

The idea that this period of observation might become too long was considered in the third case of this series. This patient was a 26-year-old white male, who, on arrival overseas, suffered from abdominal cramps, nausea, and vomiting. A short period of hospitalization resulted in relief, and discharge from medical care. Several episodes of similar character occurred, and after a particularly acute period of severe abdominal pain, a diagnosis of acute hemorrhagic pancreatitis was made. Celiotomy was performed, and an abscess involving the pancreas and lesser sac was encountered, incised and drained. The patient did well after operation, but a pancreatic fistula was noted shortly after surgery, which persisted to the time of admission to our hospital.

Examination revealed little except marked emaciation and weakness. A fistula from which pancreatic fluid was flowing was found in the left subcostal area.

The results of laboratory examinations showed R B C 4,280,000, Hb 12 4 Gm, W B C 6,200, hematocrit 38 8 per cent, sed rate 0 6 Mm/min, N P N 28 9 mg per cent, serum protein, 6 85 Gm per cent, sodium 140 6 m eq/L, chloride 103 0 m eq/L, carbon dioxide combining power 31 2 m eq/L. These findings with the exception of a moderate degree of anemia and elevation of  $\text{CO}_2$  combining power are within normal limits.

After completion of clinical and laboratory observation, decision was made to subject this individual to surgical exploration and correction of the fistula. The period of observation and preparation had been 21 days. This



FIG. 4—Collecting apparatus applied to patient



decision was based upon several facts, the chief of which was that the fistula had been present for about five months. Second, the clinical laboratory studies demonstrated findings within normal limits. Third, sufficient time had been allowed for spontaneous closure to have occurred under these favorable circumstances. Fourth, there was considerable doubt in our minds as to the validity of the original diagnosis for: 1. There had been gradual rise in the left leaf of the diaphragm, as demonstrated roentgenologically. 2. A palpable mass had appeared in the upper abdomen. 3. The youth of the patient, coupled with the total absence of any previous related illness, suggested the impression of a previous error in diagnosis, as the expected appearance of acute pancreatitis in an individual of this age and build would be statistically low.

A transverse incision was made in the upper abdomen encircling the external orifice of the fistula after which dissection to the pancreas was facilitated by following the course of the tract. The lesser sac was entered through an aperture in the gastrocolic omentum near the greater curvature of the stomach. The pancreas was found to be enlarged, firm and rubbery in consistence. There were no individual masses in the pancreas, and its texture was similar throughout the entire length. The dissection of the fistulous tract was resumed, following this exploratory palpation, and it was found that it continued into the head of the gland. Because of the small internal diameter of the fistula, and the fact that an opening into the digestive tract need not be made if transplantation were not effected, the procedure of choice seemed to be ligation of the tract as close as possible to the pancreas and subsequent excision of the fistula. This was done, and when the tract was cut across at its proximal end a moderate amount of amorphous calcareous material was discovered and enucleated. The gastrocolic omentum was repaired by suture, and the wound closed in the usual manner.

The postoperative course was smooth for the first week. Then the patient complained of moderately severe pain in the upper abdomen, and this complaint was associated with an elevation of temperature to 102.8° F. Examination of the wound revealed the discharge of a small amount of caseous necrotic material. This persisted and heralded the recurrence of external pancreatic flow, which was noted five days after the original symptoms of abdominal pain. The amount of fluid excreted was small and gradually decreased under a dietary regimen high in fat and low in carbohydrate content. Ephedrine and sodium bicarbonate were administered orally. Complete cessation of flow was finally achieved although, subsequently, a slight flow was again noted for a short period. Complete closure was finally obtained, and at present the wound has been entirely healed for a long enough period that recurrence would seem very unlikely. The patient is entirely ambulatory, and has regained his usual weight.

This case is exemplary of those patients with fistula whose tracts do not close spontaneously when physiologic conditions apparently are at, or are near, an optimal state for healing to occur. It is felt that the calcareous

material removed at operation was a definite factor in keeping the fistula open, and that, if it were not removed, that drainage might have persisted for a much longer time. More complete recognition of the difficulties of a prolonged period of illness and the entailed economic upset, may induce the performance of operative procedure at a time when the patient has been fully prepared and a sufficient length of time allowed to pass to permit spontaneous closure.

Certain conclusions regarding the patients and their care should be emphasized.

1 Attention should be directed toward a correction of the disturbed electrolyte content of the plasma. Reemphasis is placed on the loss of large amounts of sodium and bicarbonate ions in the pancreatic juice.

2 Dehydration is effected by two agencies. Fluid is lost through the fistula, with base, and in an attempt to preserve plasma ionic equilibrium acid radicals are excreted through the kidneys, and of necessity are accompanied by water. The administration of alkaline fluids, such as sodium bicarbonate solution, is not requisite to correct this abnormal state. Physiologic saline will provide the base while the bicarbonate ion, which is produced as an end-product of cellular metabolism, is conserved in the blood stream.

3 As in other conditions in which the economy of the body is greatly affected, hematocrit determinations and erythrocyte counts are helpful in evaluating hemoconcentration only when combined with clinical observation and other laboratory data. Alone, they are of little value and may be misleading where an anemia and severe dehydration are coexistent.

4 Anemia is a striking feature of patients who are afflicted with the more severe types of fistula, as was encountered in our first case. Whole blood must be administered when necessary.

5 The lost pancreatic fluid should be collected and after being flavored, with grape juice for instance, given to the patient to drink. The fluid is ideal for replacing the lost electrolytes.

6 The best type of diet seems to be one which is high in fat and low in carbohydrate content, as flow apparently tends to be reduced in volume when patients are on this regimen. The various vitamins, especially A, B<sub>1</sub> and calcium, should be provided in adequate amounts.

7 The use of ephedrine is justified in these individuals. A definite decrease in external flow resulted from the administration of this drug.

8 An effective method for protection of the skin must be provided. A combination of the mechanical device which was described earlier and aluminum paint has been found to be quite effective in achieving this end.

9 The surgical procedure of choice must be dictated by the individual circumstances. It is our particular feeling that a conservative course, with attention to the many aspects of metabolism, will result in spontaneous closure of the fistula in the majority of cases. If, after a sufficient period with the patient in an optimum condition, the fistula has not closed, surgical intervention is justified.

# PRIMARY GASTRIC RESECTION FOR PERFORATED GASTRODUODENAL ULCERS

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EVERY WELL PREPARED SURGEON has a routine method for performing a stated operation, but he does not restrict himself to a routine operation for a given lesion. Thus, he is prepared to vary his operation for the removal of a diseased gallbladder or an ulcer of the stomach, for instance, according to the exigencies of the case.

However, in this country a review of the literature shows that this has not been the case in the surgical treatment of acute perforations of gastroduodenal ulcers. The treatment for this has been routine, namely, suture of the perforation and closure of the abdomen with or without drainage. Some few surgeons once advocated occasional gastro-enterostomy to relieve constriction resulting from closure. But as Sallick wrote in 1936 "In this country gastric resection for acute perforation is rarely advised."

The reasons for simple closure as often put forth by conservative surgeons and expressed by Graham are "The surgeon's sole responsibility is to save the patient. At this time he does not have the responsibility of curing the ulcer. Any operative procedure directed toward the cure of ulcer is unsound, meddlesome, and adds greatly to the mortality as well as to the morbidity."

He operated upon 36 consecutive cases of perforation without a death performing closure only. Sixteen of these required subsequent operations. Sallick said that 64 per cent of his cases were not relieved by simple closure. Parker's figures come exactly between these two, 50 per cent of his patients followed (in some cases for five years) did not remain well.

The first gastric resection for perforated gastroduodenal ulcer was performed by Haberer in 1929 (B. Neiss). Four years later Amos Graves wrote "The common presence of multiple peptic ulcers in German or Central European patients with perforated peptic ulcer has encouraged German and Austrian surgeons to resect the stomach primarily—such surgery not only cures the patient but is attended by a low mortality rate." He adds almost apologetically "The study—is presented for its interest and not with the intention of encouraging the institution of surgical measures which seems too radical for the successful handling of the usual type of perforated peptic ulcer encountered in North America."

However, after presenting the good results of 144 cases from Schmieden's Clinic and 4,258 additional, he was compelled to this conclusion "Resections in good-risk Central European cases is probably justified because"—

1. The ulcers are multiple in 30 per cent of perforations
2. Gastritis is usually present

- 3 The pathologic condition cannot be evaluated by inspection and palpation alone
- 4 Resections there are performed in 40-75 minutes
- 5 Mortality is not over 5 per cent
- 6 Technically easier than in elective cases of peptic ulcer
- 7 Simple methods do not always cure and are frequently followed by recurrences
- 8 Resection later, in failures, carries a high mortality

A few comments on the above points favoring resection are in order. The first, of course, is the reason why some patients are operated upon for a perforated ulcer a second and third time when only simple closure is effected. Lang reported five deaths due to a second perforation that had been overlooked and two deaths from late postoperative perforation of another ulcer. Most surgeons now admit the second point in all gastric ulcers. Third, it is true that the perforation may be through a carcinomatous ulcer. As for the time required for primary resection, Serge Yudin ("Judine" in French Journals) reported in 1933 that of 212 cases of perforated gastroduodenal ulcers in his clinic, 168 resections were performed with a mortality of 6 per cent. Of these he operated upon 60 per cent. The other 40 per cent were operated upon by his assistants "some even by young interns." The usual time required in my cases was close to two hours—and still no deaths resulted. Time is not so important as the anesthesia and postoperative care. Reasons six, seven, and eight given above are admitted by the conservative surgeon.

The list of European surgeons who prefer primary resection for perforated gastroduodenal ulcer is a long one. Of course, they select their cases, and that shows that they are not restricting themselves to a routine procedure for this lesion. The same factors influence the mortality rate for resection as for simple suture. Yudin states that the number of hours elapsing after perforation is not the only deciding factor. He would resect in the case of a young person after 48 hours, whereas he would not resect in the case of an old patient even if the perforation were only two hours old. He selects those under 45 years of age for resections.

Friedman, Dreuter, Kuechel, and Richard favor radical operation in perforations up to six hours and not after nine hours. Some surgeons are guided by the degree and extent of the peritonitis, and some by the general condition of the patient. Yudin stresses the virulence of the infection. Hans Neuffer concluded that a case resected within the first four hours has the same chances as one resected for chronic ulcer. His time limit for resection is ten hours and the age limit fifty. He emphasizes the need for selection. It would seem to the author that the virulence of the infection may be extremely important because of the loss of one patient, age 45, in less than 24 hours after simple closure, nine hours after perforation. Niess, from Schmeiden's clinic, found no relation between mortality and duration of symptoms. His figures were

Less than 6 hours	40 patients	3 deaths
6 to 12 hours	15 patients	1 death
12 to 24 hours	5 patients	0 deaths

The statistics from clinics where simple closure of a perforation of a gastroduodenal ulcer is done as a routine show higher mortality figures for comparable cases. Therefore, let us examine the age-group that might be chosen for resection. DeBakey's review showed that the mortality of the cases sutured in the fourth decade was 18.9 per cent, in the fifth it was 28 per cent. Likewise, the deaths resulting in those perforated for only six hours totaled 10.5 per cent, seven to twelve hours totaled 21.4 per cent.

Graves' collected cases showed 5,589 simple closures with 1,450 deaths, or 25.9 per cent, and for 2,392 gastrectomies, 321 deaths, or 13.4 per cent. Of course, the latter were selected cases, but it is my thesis that gastrectomy by selection does not jeopardize the patient's life.

If, therefore, it can be shown that primary resection is as feasible in America as in Europe without jeopardizing the patient's chance for recovery and at the same time cures him of his ulcer, the dictum of the conservative surgeon may be forgotten. As for history, symptoms, signs, and laboratory findings in this series, they conform to those of the large series.

Continuous spinal anesthesia with novocaine is the anesthetic of choice today. Postoperative treatment was the same as for a routine gastric resection. Sulfanilamide and sulfathiazole, three to four grams of each, are left in the abdomen. Wangenstein's tube, with suction, is left in as long as necessary. Intravenous glucose, amino-acids, vitamins and transfusion are administered. Water by mouth is usually given after 48 hours. Usually the wound is closed without drainage.

In the author's series there was one case of postoperative pneumonia and two of wound dehiscence, one of which was followed by a ventral hernia which has since been repaired.

The present series consist of 12 consecutive cases, all males, from March 9, 1939, to March 11, 1943. It includes eight resections and four sutures, and starts with a resection. Up to this time I had followed the traditional dictum of being content with primary suture only, with one exception when I had added a gastro-enterostomy.

It so happened that the first case of the series was a man age 60, an age commonly considered too old for primary resection. But this patient had had a perforated peptic ulcer sutured 14 years previously, had been on ulcer treatment most of the time since, and had only recently left another hospital where his doctor had discharged him as "cured" after the "drip" treatment. He had been sent to Mt Sinai Hospital for roentgenologic examination of his stomach by another doctor and had arrived too late. He was put to bed and given a test meal, which showed a free acid of 48-80 and a total acidity of 35-120. That night while in bed in the hospital he was seized with sudden severe upper abdominal pain and vomited. Examination

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CASE	No	Age	Date	Symptoms	Anesthesia	Operation	Pathologic Findings	Course	Result
1	60	3/9-3/23/39	14 years ago perforation sutured one year later and persisted in hospital	Rupture	N <sub>2</sub> O O <sub>2</sub> E	Polya resection—2 hours, 15 minutes	Much free fluid in diameter Anterior wall perforation Chronic subacute gastritis with marked scarring Chronic polypoid gastritis Regional peritonitis	1 Transfusion Uneventful	Well
2	30	1/1-4/15/39	Indigestion 3 months Restricted diet Severe abdominal pain and nausea No vomiting Six hours before admission doctor gave dilaudid 2 1/2-3 weeks ago epigastric cramps Diarrhea 3-4 hours after meals Sudden severe cramp tonight while eating		N <sub>2</sub> O O <sub>2</sub> E	Polya resection—2 hours	Anterior stomach wall Perforation 3 Mm in diameter Peptic ulcer Chronic hypertrophic gastritis Regional peritonitis Chronic Duodenal perforation Chronic and subacute duodenitis Chronic polypoid gastritis Regional organizing and acute fibrinopurulent peritonitis	Uneventful	Well
3	43	12/5/40-1/21/41	Indigestion 6 years and ulcer treatment X-ray negative Pain in abdomen in afternoon Consulted doctor. Sudden severe pain in abdomen and right shoulder 2 hours previous to admission		N <sub>2</sub> O O <sub>2</sub> E	Polya resection—2 1/2 hours Sulfathiazole	Perforation 5 Mm in diameter Peptic ulcer Subacute and acute gastritis and local peritonitis	Postoperative pneumonia	Well
4	37	1/4-1/31/41	Indigestion one year Seven hours ruptured		N <sub>2</sub> O O <sub>2</sub> E	Sutured Sulfanilamide	2 ulcers 1 perforated 6 Mm in diameter Prepyloric Generalized peritonitis Streptococcus and B coli Peritoneal cultures	Uneventful	Died less than 24 hours after admission
5	45	7/17-7/18/41	Onset 8/17/41 with pain in upper abdomen Midnight 8/18/41 pains grew worse and involved whole abdomen ? Hrs ruptured? Gastro-intestinal complaint 10 years General abdominal pain since yesterday General abdominal pain last night Indigestion in past Pain recurred at work with tenderness		Novocaine Spinal 75 mg Novocaine	Polya resection Sulfathiazole	Perforation 5 Mm anterior surface prepyloric ulcer 2 cm 1 polypus Chronic subacute and acute gastritis Regional peritonitis Blood pressure 80/60 Rose 12/19 to 110/70 Gastric ulcer, anterior surface	Blood chemistry normal 2/18 T 104 4/14 T 98	
6	31	8/19-9/12/41	Several months abdominal pain after meals Severe pain shortly before admission Hematemesis 1 month previous Acute abdominal pain 12 hours		N <sub>2</sub> O O <sub>2</sub> E	Suture of perforated ulcer Sulfanilamide	Chronic and subacute gastritis Chronic and acute peptic ulcer 3 cm in diameter Perforation 7 Mm, Regional peritonitis	Uneventful	Wound rupture and resutured 12th rib resected for drainage of subphrenic abscess Had delirium tremens Icterus index 41 3/16 index 121
7	65	12/18-12/23/41	Indigestion one year Seven hours ruptured		Continuous spinal Novocaine	Polya resection	Prepyloric ulcer Marked peritonitis and eirrhosis liver, confirmed by biopsy	Blood chemistry normal 2/18 T 104 4/14 T 98	Temperature elevation 16th day Normal 22nd day Discharged 28th day
8	39	4/6-4/24/42	Indigestion one year Seven hours ruptured		Continuous spinal	Polya resection	Chronic and acute gastritis Chronic and acute peptic ulcer 3 cm in diameter Perforation 7 Mm, Regional peritonitis	Uneventful	
9	22	5/11-5/22/42	Indigestion one year Seven hours ruptured		Continuous spinal	Polya resection	Chronic and acute gastritis Chronic and acute peptic ulcer 3 cm in diameter Perforation 7 Mm, Regional peritonitis	Uneventful	
10	52	11/22/42-1/8/43	Indigestion one year Seven hours ruptured		Continuous spinal	Polya resection	Chronic and acute gastritis Chronic and acute peptic ulcer 3 cm in diameter Perforation 7 Mm, Regional peritonitis	Uneventful	
11	38	3/11-3/17/43	Indigestion one year Seven hours ruptured		Continuous spinal	Polya resection	Chronic and acute gastritis Chronic and acute peptic ulcer 3 cm in diameter Perforation 7 Mm, Regional peritonitis	Uneventful	
12	25	3/11-4/8/43	Indigestion one year Seven hours ruptured		Continuous spinal	Polya resection	Chronic and acute gastritis Chronic and acute peptic ulcer 3 cm in diameter Perforation 7 Mm, Regional peritonitis	Uneventful	

revealed the usual generalized board-like rigidity and tenderness most marked in the upper abdomen. He was operated upon less than two hours later. Much free fluid was found in the abdomen and a perforation about 8 Mm in diameter in the anterior wall of the stomach in the prepyloric region. A typical Pólya resection was performed. The pathologist reported a chronic peptic ulcer 13 Mm in diameter, chronic and subacute gastritis with marked scarring, chronic polypoid gastritis, and regional peritonitis. Nitrous oxide, oxygen and ether was the anesthetic. The operation required two hours. The patient was given one transfusion postoperatively. Recovery was uneventful and the patient is well and happy today and not restricting his diet.

Twenty-three days later, April 1, 1939, I had occasion to operate upon my next case of perforated peptic ulcer. This time the patient was a strong man, age 30, who had ruptured about six hours previously. It was only logical to conclude that if the old man of 60 did well I had a better chance with this young man of 30, although the perforation was older. His doctor telephoned me his patient had severe abdominal pain and that he had given him dilaudid twice without relief. To further questions he said the patient had had indigestion for three months and had been on a restricted diet. His pain came on suddenly. I told the doctor to send the patient into the hospital at once because it sounded like a perforated peptic ulcer, and I notified the hospital to prepare the operating room. The patient was operated upon within one hour after admission. Again, a Pólya resection was performed with excellent result. He left the hospital well on April 15, a sojourn of two weeks.

After this auspicious start I no longer felt bound by conventions. Table I shows the sequence and gives the essential information. Inasmuch as there were no deaths in the gastrectomy cases no criticism can be made that the results might have been better with suture alone. No one's life was jeopardized or sacrificed. All cases were cured both of their perforations and their ulcers. Their convalescence was not so long nor so limited in diet as is usually necessary for the cure of ulcer. The average hospital stay was 23 days, the shortest was 11 and the longest (due to a postoperative pneumonia) was 47 days.

On the other hand, gastric resections were not performed as routine as witness the four cases of suture only. In fact, I believe that my judgment was correct in selecting these cases for suture because three of them died and if resected, gastrectomy would have been blamed. As it happened none fitted the required conditions for gastric resection. These four show that it is not just one element alone which is the deciding factor in all cases. Case 5 was 45 years old, and had perforated at least seven hours before admission to the hospital. He was adjudged toxic, had two ulcers, one perforated, and had streptococcus and *B. coli* in culture from the peritoneum. He died in less than 24 hours. The second, aged 65, had perforated over 12 hours. The third fatal case was only 38 years old, but had a large cirrhotic liver, proved

by biopsy. He developed delirium tremens and jaundice postoperatively, and died in five days. He was operated upon in the early hours of the morning, immediately before Case 12, a Negro, age 25, the last resection case of the series. The fourth suture case was age 52, an alcoholic who also developed delirium tremens, then a wound dehiscence which was resutured, and, finally, a large subphrenic abscess which was drained. He recovered. I am sure not even the European surgeons would have resected anyone of these four.

Therefore, I think it can safely be said that in selected cases primary resection for perforated gastroduodenal ulcers offers the patient a cure of his disease, it saves him further ulcer treatment and second operation. It removes the danger of another perforation, and it does not increase the operative mortality above that of simple suture. It does not add to his morbidity. He is soon on an unrestricted diet. It should supersede routine suture in younger patients in good condition.

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# ATRESIA OF SMALL INTESTINE\*

TWO CASE REPORTS, ONE MULTIPLE ATRESIA, WITH SURVIVAL

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ATRESIA OF THE SMALL INTESTINE is a relatively rare condition, occurring once in every 20,000 births, according to Webb and Wangenstein<sup>1</sup> Recoveries following surgical intervention are still more infrequent Fochens,<sup>2</sup> in 1910, reported the first successful case, and Webb and Wangenstein,<sup>1</sup> in 1931, were able to collect only nine instances of survival from the literature Ladd,<sup>3</sup> in 1933, collected 14 successful surgical cases

In 1941, Ladd and Gross<sup>4</sup> reported seven recoveries in 52 personal cases treated surgically at the Children's Hospital in Boston Cole, in discussing Ladd's<sup>3</sup> paper in 1933, recorded seven cases of atresia of the intestine at the St Louis Children's Hospital Four of these were treated by anastomosis and three by ileostomy, but none survived

Atresia results from an arrest in development in the second or third month of fetal life This is a failure of recanalization of the intestinal tract following the obliteration of the original lumen between the fifth and tenth week by epithelial concrescences

The sites of atresia in Ladd's<sup>4</sup> 52 cases were In the duodenum in 5, jejunum in 6, ileum in 34, ileocecal valve in 2, colon in 2, and multiple in 3 Our successful case was multiple atresia of the jejunum, and the other occurred in the midportion of the small intestine or beginning third of the ileum As far as we know, this is the second case of survival of multiple atresia of the small bowel The first case was reported in November, 1943, by Duncan, *et al*<sup>5</sup>

Attention is directed to the condition by persistent vomiting and lack of normal meconium Ladd<sup>4</sup> stressed the fact that the examination of the stools may be of aid in determining the presence of a complete occlusion Normal meconium contains keratinized epithelium from vernix caseosa in swallowed amniotic fluid This epithelium is easy to recognize (Farber's test) and obviously is absent when complete obstruction exists

Distention may or may not be a factor In atresia of the duodenum or high jejunum, it is absent or negligible

The most valuable laboratory test is a plain film of the abdomen This shows distended loops of bowel and step-ladder levels in the erect posture Some additional information is obtained in having a roentgenogram taken in the head-down position Barium by mouth or rectum gives little further

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diagnostic aid. Furthermore, it is not without danger, because the barium might clog the narrow lumen of the distal loops following anastomosis. A greater danger is that of bronchopneumonia following aspiration of the vomited barium. Autopsies revealed bronchopneumonia in a high percentage of the unsuccessful cases.

The differential diagnosis is not difficult. The two conditions which most nearly simulate it are atresia of the esophagus and imperforate anus. The inability to pass a stomach tube will identify the first, and simple inspection the latter. Pyloric stenosis, as a rule, occurs later in life. Obstruction due to malrotation is not usually complete, and furthermore, celiotomy is indicated in both conditions, so little harm results from mistaking one for the other.

The possibility of the aspiration of gastric contents necessitates gastric lavage as a preoperative measure, or one might consider inserting an intubating gastric tube. Naturally, preoperative treatment includes liberal administration of parenteral fluids.

With this brief résumé of the condition, we wish to report the following two cases. For those especially interested, we recommend the articles by Webb and Wangenstein,<sup>1</sup> and Ladd,<sup>3</sup> and the chapter on congenital atresia of the intestine and colon in Ladd and Gross' "Abdominal Surgery of Infancy and Childhood."<sup>4</sup>

#### CASE REPORTS

**Case 1**—P. H. is a colored male child whose birth was in every way normal. One hour following all feedings he vomited, and at the end of 36 hours had been unable to retain anything. He never passed meconium but had a stool which appeared to be an intestinal cast containing no lumen. The vomitus was bile-stained and projectile in type. Repeated enemas were ineffectual for fecal matter nor did they relieve the distention, which was prominent. Visible peristalsis was noted crossing the abdomen and, on auscultation, high-pitched tinkles were heard. Roentgenologic studies revealed an obstruction in the upper portion of the small bowel with marked distention of the stomach and duodenum.

After preparation with repeated hypodermoclyses of saline and glucose solution, plasma intravenously and gastric aspiration, the child was operated upon at about the 64th hour of life, February 15, 1943. Preoperatively, he was given atropine sulfate, gr  $\frac{1}{1000}$ . Open-drop ether anesthesia was used. The abdomen was opened through a left rectus incision. At a point approximately ten inches from the ligament of Treitz, the obstruction was encountered in the form of an atresia. Distal to this were found three sausage-shaped loops of bowel, blind at both ends and measuring 2.5, 2 and 6 cm in length. Each segment had its own solitary blood supply. The distal loop appeared to be connected with the ileum, and this was simply ligated with one piece of No. 000 catgut. An open side-to-side isoperistaltic anastomosis was carried out between this markedly distended jejunum and the completely collapsed ileum, using No. 00000 chromic catgut throughout. The abdomen was closed in layers without drainage.

Postoperatively, the patient received frequent hypodermoclyses of glucose and saline solution. Fifty cubic centimeters of plasma were given intravenously for two days. Twelve hours following operation, the temperature rose to 107° F. but fell to normal on the following day. A small abscess at the site of a retention suture was probably



FIG 1 —(A) Plain film of Case 1 (P H), (B) erect position, and (C) head down position

responsible for spikes of temperature up to  $102^{\circ}$ – $103^{\circ}$  F during the first five days. Following this, it remained normal. Because of the rather marked jaundice, vitamin K was given parenterally as a prophylactic measure for hemorrhage. On the third postoperative day, the baby was started on breast milk, one-half ounce every two hours. Two bowel movements occurred on the fourth postoperative day. After this, improvement was rapid. He was discharged from the hospital on his 28th day of life in good condition.

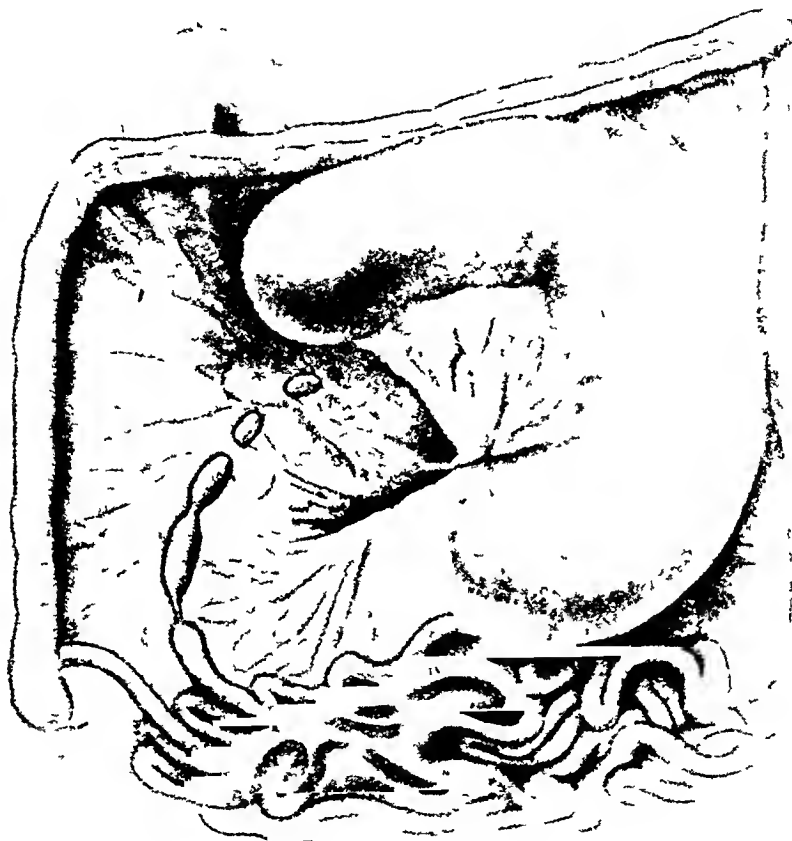


FIG. 2.—Drawing of findings at time of operation in Case 1 (P. H.)

On March 25, 1944, the baby weighed 14 pounds 10 ounces, and although he could not sit up alone, generally, he seemed fairly alert. He has occasional episodes of vomiting, and a gastro-intestinal roentgenogram showed a certain amount of hypomotility of the small intestine with some pooling of barium at what appeared to be the site of the anastomosis. However, this had all passed into the colon at the end of 24 hours. No trace of the barium could be seen on a plain film six days later.

**Case 2**—F. W. was a colored male child whose birth was normal. On the second day of life, his abdomen became distended, but vomiting did not occur. Peristalsis was hypo-active. Digital examination revealed no obstruction low in the rectum. An enema was effectual for only a small amount of mucinous material. Roentgenologic



FIG 3 — (A) Plain film of Case 2 (F W), (B) erect position (note air under diaphragm), and (C) head down position

study revealed marked distention of the small bowel down as far as the ileum. Air was noted beneath both diaphragms, suggesting a probable perforation.

Preoperative preparation consisted of saline and glucose solution by hypodermoclysis, vitamin K parenterally and gastric aspiration. Under open-drop ether anesthesia, the abdomen was opened through a left rectus incision. A moderate amount of faintly-cloudy fluid was encountered, and air was noted to escape as the peritoneum was opened. An atresia was found in the midportion of the small bowel. The proximal loop was greatly distended and parts of it covered with a yellowish fibrinous exudate, but no site of perforation could be detected. The proximal and distal loops were approximated and a side-to-side isoperistaltic open anastomosis was done, using an inner layer of No 00000 chromic catgut and an outer layer of arterial silk. The abdomen was closed in layers without drainage.

Postoperatively, jaundice became prominent. Despite the administration of parenteral fluids, one transfusion, vitamins K and C and repeated gastric aspirations, the temperature gradually rose to 104° F, and the patient died 46 hours later. Autopsy revealed death to be due to bronchopneumonia and possibly shock. There was no evidence of peritonitis.

**DISCUSSION**—As in intestinal obstruction due to any cause, early recognition of the condition lowers mortality. Therefore, the result of surgery depends primarily upon the astuteness with which the pediatricians diagnose the case and the promptness with which it is brought to surgery.

*Anesthesia*—In our two cases, the suggestion of Ladd and Gross<sup>4</sup> in using open-drop ether was followed. Local anesthesia might be considered, but the anastomosis is of such a nature as almost to demand a quiet operative field.

*Operative Technic*—One of our main reasons for presenting these two cases is to emphasize the need of performing a primary anastomosis. On opening the peritoneum, the discrepancy in size between the collapsed loops of bowel and distended bowel is so great that anastomosis seems to be a technical impossibility. Only the insistence of Ladd and Gross<sup>4</sup> that this is the only procedure that offers any hope for survival made us attempt it in our first case.

Ileostomies have probably been the most commonly employed procedure, but the results have been almost invariably fatal. The only two successful cases reported<sup>3, 6</sup> in which this technic was employed were done for atresia in the terminal ileum. The higher in the small intestine the atresia is, the greater is the electrolytic imbalance resulting from the loss of intestinal contents through an enterostomy. The primary ileostomies probably did very little to facilitate secondary anastomoses, one of which was done within two months and the other 30 days following the original procedures.

The distal lumen is so narrow that Wangenstein<sup>2</sup> has suggested dilating it by injecting it with saline. Ladd and Gross<sup>4</sup> have used a small catheter for dilatation. We used neither of these suggestions, but in our successful case we did not put in a second anterior layer for fear of so inverting the mucosa as to occlude the lumen.

Fine suture material is essential. In the first case, No 00000 catgut was used throughout. The ideal suture material is arterial silk for the serosal layer and No 00000 catgut on a swedged needle for the mucosal layer.

Our second case, in retrospect, might have had a better chance of survival had our intravenous administration of blood or plasma been more vigorous. These are long procedures, and infants are subject to shock just as adults are. We are inclined to neglect this point, possibly because intravenous therapy is difficult in the newborn. Anemia should be corrected by the administration of blood in the amount of 5-8 cc per pound of body weight. It is well to keep in mind that the loss of 30 cc of blood in an infant is equal to about 500 cc in an adult. Body heat can be conserved by placing a hot water bottle under the child's back during the procedure.

The transient hypoprotrombinemia of the newborn leading to hemorrhagic tendencies is now common knowledge. Disorders of the gastrointestinal tract, such as pyloric stenosis or obstruction due to atresia or malrotation, are particularly prone to develop hypoprotrombinemia.<sup>7</sup> One of the cases of atresia reported by Webb and Wangenstein<sup>1</sup> died of postoperative hemorrhage from the wound and into the peritoneal cavity. This not infrequent fatal postoperative complication can best be treated by the specific prophylactic administration of vitamin K preoperatively, the dose being 1-2 mg of one of its synthetic forms. An increase in the blood prothrombin can usually be detected within two to six hours.<sup>7</sup>

The question of sulfonamides arises. There is probably very little indication for their intraperitoneal use. Though no bacterial studies confirm the following statement, one would naturally assume that the intestinal contents in the newborn have a much lower bacterial count than later in life. Peritonitis was not a frequent cause of death in reported cases. Bronchopneumonia was the most common finding at autopsy.

#### SUMMARY

Two cases of intestinal atresia treated by primary anastomosis have been reported, one being the second successfully treated case of multiple atresia.

The unsuccessful case was technically satisfactory, and more vigorous postoperative care might have prevented a mortality.

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# CAUDA EQUINA COMPRESSION SYNDROME WITH HERNIATED NUCLEUS PULPOSUS

A REPORT OF EIGHT CASES

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MUCH HAS BEEN WRITTEN on the subject of herniation of the nucleus pulposus in its more common form but little has been described concerning the clinical manifestations of extensive protrusions. We have had occasion recently, to observe a number of instances of this type in which the protrusions were so extensive as to produce complete, or nearly complete, subarachnoid block with cauda equina compression. The resultant anamnesis so closely simulates cauda equina tumors that most of the early cases were explored for suspected neoplasms, and it was not until the condition had been encountered on several occasions that the possibility of herniated nucleus pulposus could be anticipated. In our experience, indeed, cauda equina compression occurs much more frequently due to herniated nucleus pulposus than to tumor. For this reason, this series of cases is reviewed to evaluate the presenting clinical manifestations, means of diagnosis, operative findings and the sequelae encountered. These patients have all been observed and treated at the Strong Memorial and Rochester Municipal Hospitals during the past 18 months.

## CASE REPORTS

**Case 1**—F S, S M H No 199505. The patient was a 28-year-old housewife who, 15 months prior to admission, following a normal pregnancy and delivery, developed low back pain on the left side. She was treated for "scoliosis" with a plaster jacket which she wore for three months. The pain disappeared almost entirely until three days prior to admission when, while stooping over, she felt her back "snap." There was immediate pain in the back and down the legs, which increased in severity until admission. The day before entry, numbness of the right leg, left leg, left foot, back of left thigh, vulva, and perineum developed in that order. There was some twitching of the muscles of the buttocks. For 24 hours the patient had been unable to void spontaneously, being incontinent of small amounts of urine occasionally. There had been no bowel movements for two days. The patient was bedridden because of the pain. The past history was negative except for rheumatic fever at age 22.

*Physical Examination* This revealed a moderately obese, bedridden young woman in some pain. The general physical and neurologic examinations were not remarkable except for the following positive findings. There was a coarse nystagmus on extremes of lateral gaze. The bladder was palpable nearly to the umbilicus. There was tenderness over the fifth lumbar spine. There was no abnormal alignment of the spine with the patient recumbent, and it was not possible to have her stand. There was a marked weakness of both legs varying from minimal changes in the upper leg muscles to almost

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complete paralysis of the anterior tibial group on the left side. Anesthesia was present in the saddle area, dorsum of both feet, toes, and the sole of the right foot. Hypesthesia was present over the left sole and lateral and posterior aspects of the left leg. Position sense was impaired on the left. Both ankle jerks were absent, but the knee jerks were equal and brisk.

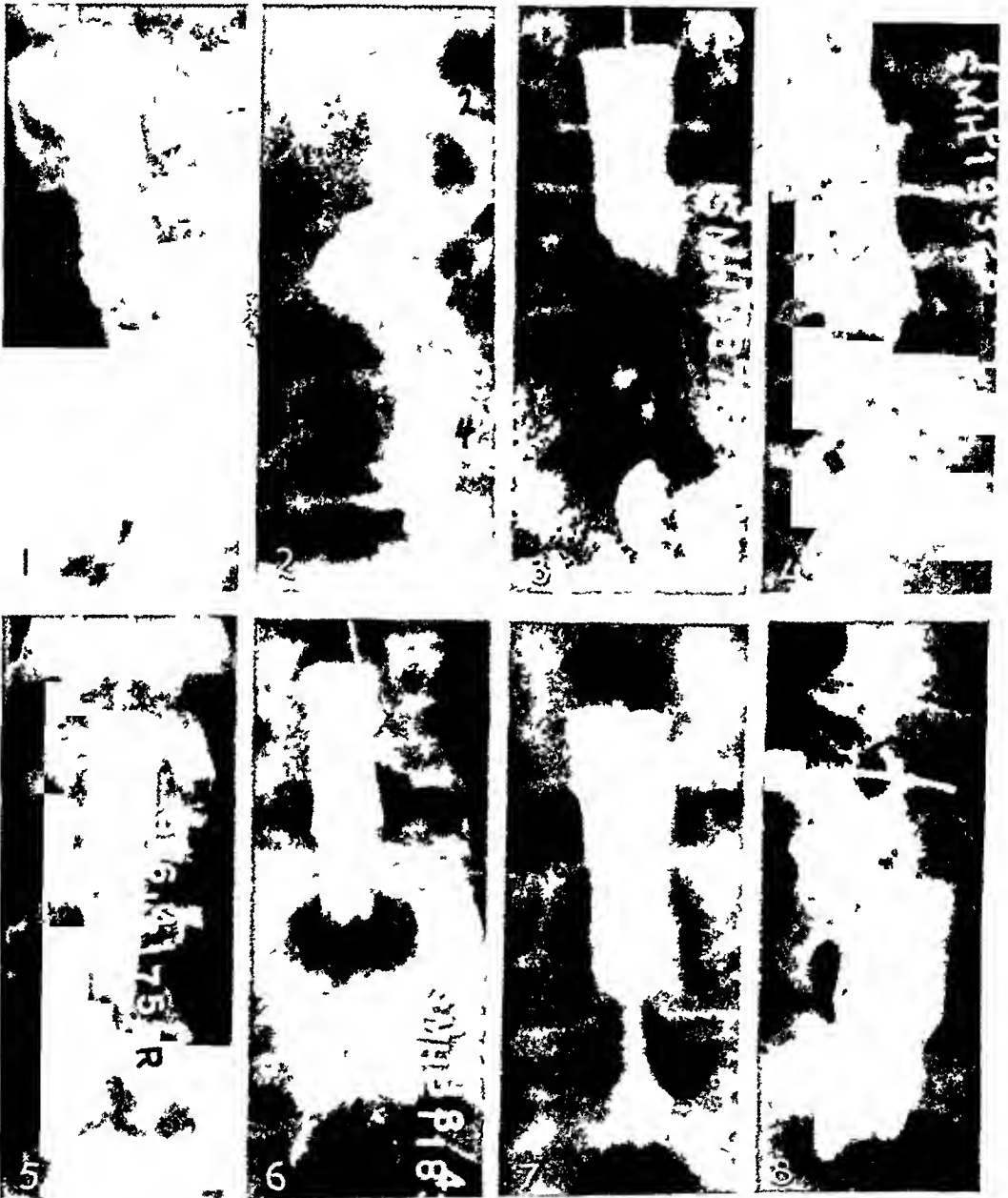


PLATE I—The myelograms of all patients are shown here. All except Case 2 were made with panto-paque. All were taken with the patient on the fluoroscope table in a nearly erect position.

*Laboratory Data* Red blood count of 47 million, hemoglobin of 15 Gm., white blood count of 13,500, with a normal differential. The serology was negative. The urine contained 3-5 white cells per high power field, and *Escherichia coli* was cultured. Lumbar puncture between the third and fourth lumbar vertebrae demonstrated normal manometrics. The fluid showed a negative serology, and a protein content of 110 mg per cent.

Roentgenograms of the lumbar spine showed narrowing of the fourth lumbar body, and the third, fourth, and fifth lumbar interspaces on the left. Pantopaque myelography demonstrated a complete subarachnoid block at the third lumbar interspace (PLATE I, Fig 1).

The patient was given sulfadiazine orally and placed on Monroe catheter drainage. On the 18th hospital day, a laminectomy was performed exposing the third lumbar interspace but no defect was seen. The dura was opened, revealing extensive arachnoid thickening with gross matting of the nerve roots of the cauda equina. Exploration with a catheter revealed an obstruction at the fourth interspace, which was subsequently explored, and a large herniated nucleus pulposus removed. The obstruction at L-3 by myelography was felt to be due to the arachnoid adhesions seen on opening the dura.

Postoperatively, the patient was free of pain. She gradually regained control of her bladder and was able to void spontaneously 15 days after operation. When last seen, eight months after operation, she had a mild residual vulvar anesthesia, but normal sphincter control. She was able to walk with the aid of a cane, there being some residual foot drop on the left.

**Case 2**—M D, S M H No 192500. The patient was a 62-year-old railroad worker who, except for 40-pound weight loss during the preceding two years, was in excellent health until three weeks prior to admission, at which time he awoke with a severe pain in his back radiating down the left leg. This pain persisted and was followed by weakness. Ten days prior to admission, numbness of the lateral aspect of the left leg was noted, and five days later, he was unable to walk because of the weakness and pain. For about a week before entry, there was some nocturia. The pain was aggravated by coughing. Twitching of the muscles of the legs and arms was reported for approximately two months. He had progressive difficulty in voiding but was still continent at the time of operation.

*Physical Examination*—This revealed a well-developed elderly man showing some evidence of weight loss. General and neurologic examinations were not remarkable except for the following positive findings. The rectal sphincter was moderately relaxed. There was bilateral weakness of all muscle groups of the legs, more pronounced on the right side and in the peroneal regions. Occasional localized twitchings were seen in the upper and lower extremities. There was sensory loss as high as the first lumbar dermatome on the right and the third lumbar dermatome on the left. Little change was noted in the sensation of the legs but the patient was not able to cooperate well enough for a very exact sensory examination. There was bilateral loss of position and vibratory sense. The left knee jerk was diminished. The right knee jerk and both ankle jerks were absent.

*Laboratory Data* Blood studies were normal except for a blood sugar of 200 mg per cent. Urinalysis revealed a glycosuria. Serology was negative. Lumbar puncture at the fourth lumbar interspace showed a complete block, with xanthochromic fluid having a protein content of 630 mg per cent. Roentgenograms of the lumbar spine demonstrated a list, with convexity to the right, narrowing of the second lumbar intervertebral space and hypertrophic changes.

Lipiodol was introduced by cisternal puncture. A complete block was visualized at the third lumbar intervertebral space (PLATE I, Fig 2). The protein content of the cerebrospinal fluid withdrawn at this time was 25 mg per cent.

The diabetes was controlled with 20 units of protamine-zinc and 10 units of regular insulin daily. On the tenth hospital day, the patient's spinal canal was explored for tumor of the cauda equina. The third and fourth lumbar laminae were removed, exposing a large herniated nucleus pulposus, which was apparent even on the dorsal surface of the dura (Fig 1). This was removed (PLATE II, Fig 1) and the dura opened, revealing matting and injection of the roots of the cauda equina together with a thickened milky-appearing arachnoid. A spinal fusion was carried out.

The postoperative course was complicated by some fecal incontinence, but motor power returned gradually. Bladder and bowel function were normal one to two months after operation. Seventeen months after operation, the patient was asymptomatic, and employed as a laborer. Both ankle jerks were diminished but there was no localized weakness or sensory abnormality.

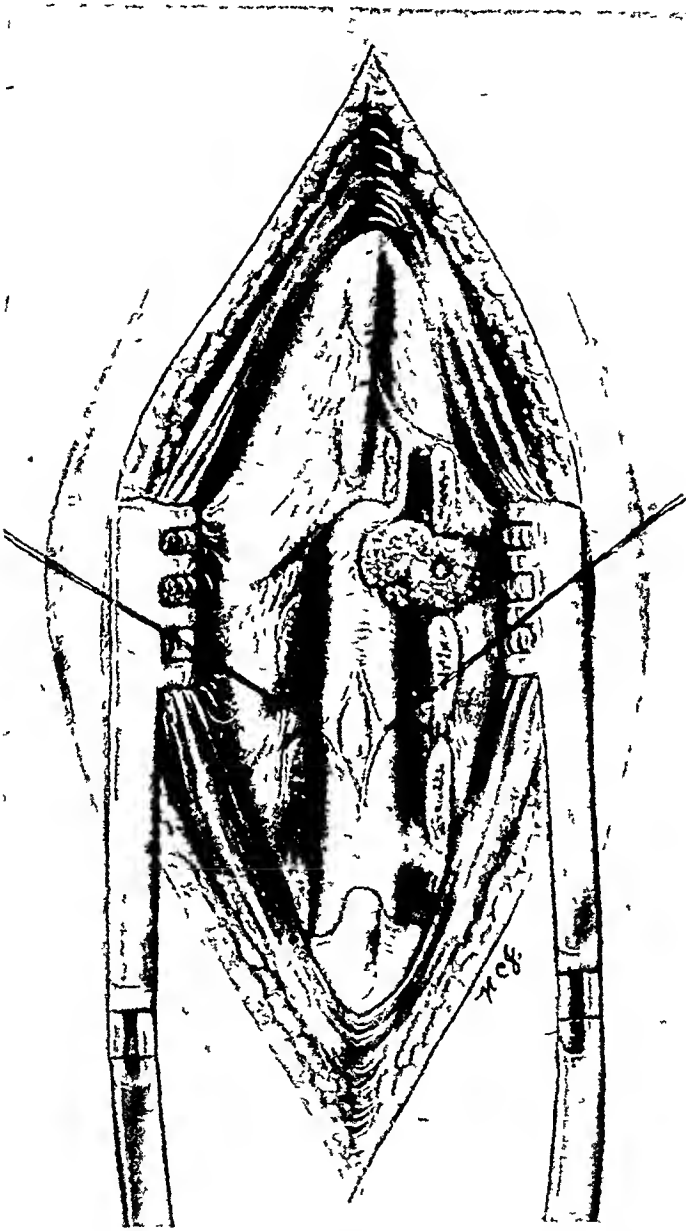


FIG 1—A diagrammatic representation of the pathology encountered in Case 2. A chordoma tumor was anticipated, which accounts for the wide exposure. The extent of the protrusion of the nucleus pulposus is demonstrated at the third lumbar interspace.

**Case 3**—A T, S M H No 187681. The patient was a 37-year-old cabinetmaker who, for 15 years, had had "lumbago," characterized by low back pain of an intermittent nature coming every three to four months and lasting two or three days at a time. Six months prior to admission, the back pain became more severe, radiating down the back of both legs (the left more than the right). Pain progressed until two

months before admission, when it was knife-like in nature. It was aggravated by coughing and sneezing. No relief was obtained from chiropractic treatments or arch supports. Some frequency of micturition and a sensation of fullness of the bladder was noted during this period, as was increasing constipation. Past history was remarkable only in that patient was reported to have had "tuberculosis of the hip" at the age of seven.

*Physical Examination*—This revealed the following positive findings. The patient was a muscular man who appeared to be in considerable pain. Movements of the back were limited in all directions although there was no definite list. Straight leg-raising was limited to 30° on the right and 20° on the left. There was measurable atrophy of the left thigh and calf. The Lasague's sign was positive bilaterally. There was a patchy hypesthesia of both legs, constantly found in the L-4 distribution on the right but noted at times as high as D-12 on the left and L-1 on the right.

*Laboratory Data* Blood studies and uranalysis were normal. The Wassermann was negative. Lumbar puncture between third and fourth lumbar vertebrae showed no evidence of block. The fluid showed a total protein content of 100 mg per cent. The spinal fluid Wassermann was negative.

Myelography with pantopaque showed a block at the midportion of the fourth lumbar vertebrae. A small amount of the contrast material trickled by on the right side (PLATE I, Fig 3).

Laminectomy was performed, and a large herniated nucleus pulposus removed from the region of the fourth lumbar interspace (PLATE II, Fig 2).

The postoperative course was uneventful. Four months after operation the patient was asymptomatic except for mild "lameness" in the back, and was working regularly.

**Case 4**—A B, S M H No 193284. The patient was a 56-year-old lastmaker, who was in excellent health until four months before admission, when he began to have severe pain in the back which would occasionally radiate down both legs. The pain increased in severity until he was forced to stop work seven weeks before admission. At this time he noticed weakness of the left leg associated with diffuse numbness on that side. Shortly before admission, the patient became bedridden by the pain. The pain was greatly aggravated by coughing and straining, by lying flat in bed, and by walking. His only treatment had been "hip-shots" and massage, from which he had no relief. For about five weeks before admission he noticed increasing difficulty in voiding, and a change in bowel habits. The past history was not remarkable.

*Physical Examination* This revealed a muscular, elderly-appearing man in apparent pain. The positive findings noted were as follows. The prostate gland was slightly enlarged. There was bilateral lumbar muscle spasm without abnormal alignment of the spine. There was tenderness over sacrum and gluteal regions, somewhat more prominent on the right side. Pain was expressed on all movements of the back and on extension of the legs at the hips. The patient walked with a limp, necessitating the use of a cane. Straight leg-raising was permitted to 75° on the right and 90° on the left. There was hypesthesia over the lateral aspect of the left leg as low as the knee and over a small patch on the lateral aspect of the right knee. Patchy hypesthesia was reported as high as D-10 bilaterally. There was 1 cm atrophy of the left leg as compared to the right. The left knee and ankle jerk were hypoactive.

*Laboratory Data* The blood count, uranalysis, and blood chemistry were normal, and the Wassermann was negative. Lumbar puncture was attempted at the fourth lumbar interspace without success. Roentgenograms of the lumbar spine showed minor degenerative changes.

Myelography with pantopaque was carried out, revealing an almost complete block at the level of the fourth lumbar intervertebral space. A small amount of the contrast material trickled by the obstruction, as shown in PLATE I, Fig 4.

Laminectomy was carried out, and a large midline herniated nucleus pulposus removed from the fourth lumbar intervertebral space transdurally (PLATE II, Fig 3).

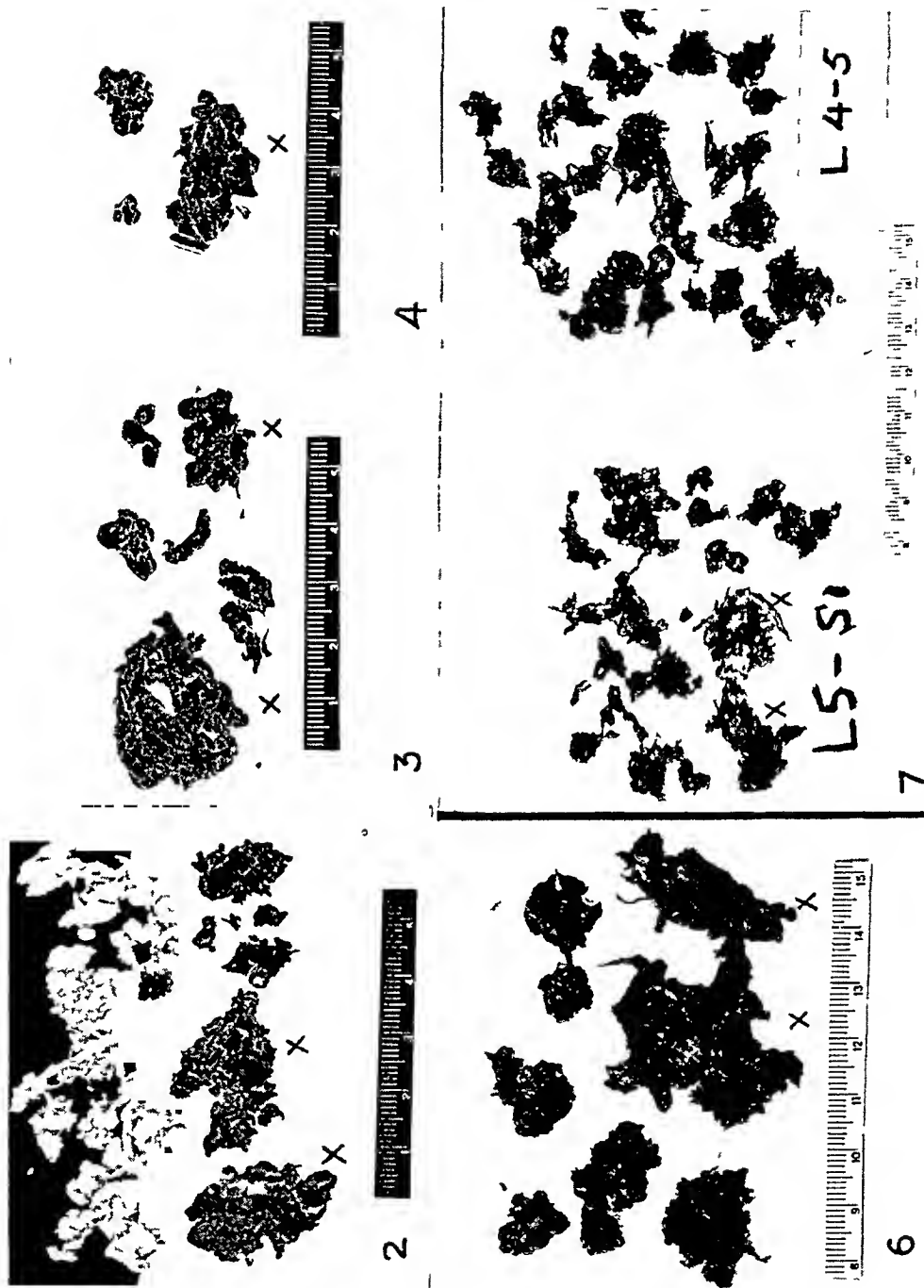


PLATE II—The material removed at operation in Cases 2, 3, 4, 6 and 7 is shown here. The larger pieces of the tissue marked X represent that portion of the nucleus pulposus extruded into the spinal canal causing the compression. The material removed from each of two interspaces is shown in Case 7

Postoperative course was uneventful, and the patient was asymptomatic three months after operation

**Case 5—J G, S M H No 181757** The patient was a 45-year-old ex-mechanic who, for 30 years, had had occasional shooting “numb sensations” down the left leg, noticed mainly after overexertion. For the past ten years, he had had five such episodes lasting approximately three days each. Two weeks before admission, coincident with a “cold” and cough, he developed severe low back pain. Two days later, the pain began to radiate down the left leg, then down the lateral aspect of the right leg, with associated numbness of both legs. He was confined to bed by the pain for two days prior to admission, and had great difficulty in urinating. The pain was sharp and shooting in character and aggravated by cough. It was not relieved by vitamin B injections, morphine, or bed rest.

*Physical Examination*—This revealed a well-developed, well-nourished man, who appeared to be in some pain. General and neurologic examinations showed the following positive findings. The teeth were somewhat carious. There were a few coarse dry râles at both lung bases posteriorly. The patient was unable to walk. The spine was straight, with slight tenderness over the sacrum and right lumbar regions. There was bilateral tenderness in the posterior thigh regions. Straight leg-raising was markedly limited because of pain. Twitching was noticed in the glutei and calf muscles. The left thigh and calf were measurably smaller in circumference than the right. There was hypesthesia over both feet, the dorsum of the right calf, lateral aspect of the left calf, and of the saddle area. Vibratory sense was absent on the left. The right knee jerk was diminished and both ankle jerks were absent.

*Laboratory Data* The blood count, uranalysis, and stool examinations were within normal limits. The Wassermann was negative. Lumbar puncture between the third and fourth lumbar vertebrae demonstrated normal dynamics, with a spinal fluid protein of 60 mg per cent.

A chest film was not remarkable. Lumbar spine films showed some deviation to the left. Myelography with pantopaque showed a sharp cut-off in the subarachnoid space at the fourth lumbar interspace (PLATE I, Fig 5).

Laminectomy was performed and a large herniated nucleus pulposus was removed extra- and transdurally. There was evidence of arachnoiditis on exploring the cauda equina, and microscopic section of the arachnoid showed round cell infiltration.

The postoperative course was uncomplicated. At the time of discharge the patient was asymptomatic. The only positive findings on physical examination were hypesthesia of the left foot and absent ankle jerks bilaterally. He did not return for follow-up.

**Case 6—E J, S M H No 311831** The patient was a 28-year-old housewife, who first noticed pain in her right leg approximately ten years before admission, three months following an automobile accident in which she sustained no known injury. This episode lasted one and one-half years. She had similar but shorter attacks six and five years before admission, and following the latter she had operations upon both of her hip regions (probably fasciotomies). Subsequently she complained of repeated episodes of right hip and leg pain, on two occasions relieved by injections in her back. The last episode started approximately six months before admission, following which mild burning pain in the entire right leg on exertion was experienced. She also complained of an occasional twinge of pain in the left leg. Approximately one to two weeks prior to admission the patient noticed more severe pain in both legs associated with paresthesias and numbness in the right leg. Three days before admission, she became unable to void.

*Physical Examination*—This revealed the following positive findings. On examination of the back, there was a list to the right, and considerable spasm of the paraspinal muscles. She experienced considerable pain on all movements of the back. Straight leg-raising was limited to 20° on the right and 30° on the left. There was 1 cm atrophy of the right calf, associated with considerable weakness of all movements of

the foot, particularly with reference to plantar flexion. Mild atrophy was also noted in the left gluteal region and upper leg. Bilateral upper lateral femoral operative scars were present and there was an area of hypesthesia over the distribution of the left lateral femoral cutaneous nerve, which the patient stated had been present since her operation five years before. Hypesthesia was noted bilaterally in segments S-4 and S-5 and on the right in segments L-5 to S-3. Almost complete anesthesia was present over the outer aspect of the right foot. The right knee jerk was diminished and the right ankle jerk absent. The patient was unable to void and had to be placed on tidal irrigation.

*Laboratory Data* Blood studies and uranalysis were normal. The serology was

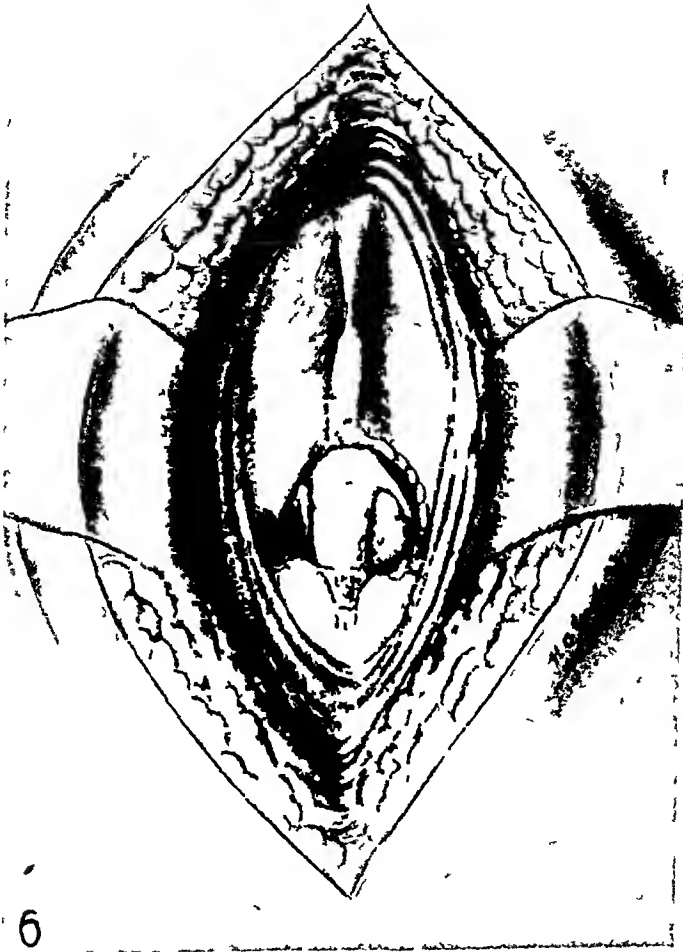


FIG. 2.—A diagrammatic representation of the pathology encountered in Case 6. The extruded nucleus pulposus is seen in the region of the fifth lumbar interspace.

negative. Roentgenograms of the spine showed narrowing of the fifth lumbar interspace. Spinal fluid protein was 90 mg per cent. A pantopaque myelogram demonstrated a complete block at the fifth lumbar interspace (PLATE I, Fig. 6).

Laminectomy was performed (Fig. 2), and a large herniated nucleus pulposus removed from the fifth lumbar interspace (PLATE II, Fig. 4).

The postoperative course was uneventful. The patient was able to void spontaneously nine days after operation. When last seen, two months after operation, she was free of all discomfort and voiding normally. There was still slight weakness of the right plantar flexors. The right ankle jerk was absent, and there was hypesthesia over the outer aspect of the right leg and foot.

**Case 7**—I B, S M H No 211100 The patient was a 43-year-old tailor, with pain in the back and both legs of seven months duration. Seven months before admission he noticed the onset and progression of pain in the low back and down the backs of both legs, associated with parasthesias, weakness and coldness. These symptoms persisted, and about two months before admission he became unable to void. Subsequently, he catheterized himself regularly. Past history was pertinent in that patient reported an episode of weakness in the legs lasting for a month in 1928, treated by injections of calcium gluconate. No history of trauma was obtained. The patient had lost ten pounds in the previous six months.

*Physical Examination*—The following positive findings were apparent. The spine showed a list to the left, with rather marked limitation of motion in all directions and spasm in the paraspinal muscles. There was some diffuse weakness of the anterior and posterior calf muscles but strength in general was quite good. Gluteal tone was very poor. There was anesthesia in the saddle area involving the S-4 and S-5 dermatomes, with a trophic ulcer on the left side in this area. There was complete retention of urine, and the rectal sphincter tone was very poor. Both ankle jerks were absent.

*Laboratory Data*—Blood count was normal, and serology was negative. Urinalysis showed pyuria, with *Streptococcus hemolyticus* and *B. proteus* being isolated. Roentgenograms showed a relative narrowing of the lumbosacral interspace. Pantopaque myelography demonstrated a marked narrowing in the visualized column at L-4, and complete block at L-5 (PLATE I, Fig 7).

At surgical exploration, a large herniated nucleus pulposus, completely compressing the dural sac, was removed from the L-5 S-1 interspace. A pathologic protrusion of the fourth intervertebral disk was also encountered and corrected (PLATE II, Fig 7).

The postoperative course was one of gradual improvement. Pain had disappeared after about three weeks, and patient first began to void spontaneously about five weeks postoperatively. At this time, cystometry showed normal bladder response. When seen four and one-half months after operation, he still had 90 cc residual after urination, and some constipation. He reported himself markedly improved but still had mild pain in the back although none was present in the legs. Hypesthesia was still present in sacral areas 3, 4, and 5, and there was mild weakness in plantar flexion on the right. The ankle jerks were absent.

**Case 8**—A B, S M H No 212371 The patient was a 36-year-old housewife. Four and one-half years before entry, she first noticed the onset of pain in the back associated with cramps and shooting pains in the left leg, increasing in severity. Three years before admission she had a severe episode of backache and pain in both legs, at which time she was studied elsewhere, and was in bed for two months. The pain was worse on coughing and sneezing. Subsequently, she was considerably improved although not completely without pain until about two months before entry, at which time the pain became progressively worse. She noticed that she would drag the right leg, and complained of numbness and tingling in the saddle area. She also noticed increasing urinary urgency and frequency, culminating in complete retention the day before entry. Past history developed that 18 years before admission the patient had her left kidney removed, apparently because of calculi. There were no subsequent urinary complaints until her admitting illness.

*Physical Examination*—The following positive findings were present. The patient was confined to bed. There was flabbiness of the glutei and weakness of all movements of the right foot, particularly in plantar flexion. There was no difference in the size of the two legs. Straight leg-raising was limited to 20° on the right and 30° on the left. Saddle anesthesia was present involving S-4 and S-5, as well as the upper portions of the S-3 dermatomes on both sides. Tenderness was present in both gluteal folds. Both ankle jerks were absent. There was an old left flank operative scar.

*Laboratory Data* Blood count and urinalysis were normal and serology was nega-



tive Complete urologic studies revealed a normal functioning right kidney and an absent left kidney. Roentgenograms of the abdomen showed many calcified nodes on the left side. Cystoscopy showed a small projection of tissue at the vesicle neck (later removed) and some trabeculation of the bladder. Urine culture yielded *B. proteus* and *B. pyocyaneus*. Roentgenograms of the lumbar spine showed a relative narrowing of the fifth lumbar interspace. Spinal fluid protein was 200 mg per cent, although a few red blood cells were reported present. Pantopaque myelogram shown in Plate I, Fig 8.

At surgical exploration, a large herniated nucleus pulposus, completely compressing the dural sac, was removed from the lumbosacral interspace. Her postoperative course was uneventful. She began to void spontaneously approximately three weeks after operation. Four weeks after operation, she was ambulatory, without pain. The saddle hypesthesia had definitely diminished and she was able to walk easily. There was still some weakness of the right foot, and the ankle jerks were absent. Nine weeks after operation a letter from the patient reported mild stiffness in the back only, in spite of the fact that she was doing heavy housework. She reported herself otherwise in excellent condition.

DISCUSSION—Relatively little is known concerning the incidence of extensive herniations of the nucleus pulposus because few cases have been reported. Camp,<sup>1</sup> in 1939, using lipiodol myelography, found that in 194 cases of proved "disks," 11.3 per cent had a partial block and 2.6 per cent complete obstruction of the subarachnoid space. In our experience, of 90 verified cases of herniated nucleus pulposus, there have been eight instances of subarachnoid block, as manifested by myelography, or an incidence of 8.8 per cent.

Other cases are reported in the literature, either singly or as illustrative examples. Dandy,<sup>2</sup> in 1929, reported two cases of block due to "loose cartilage" in the lumbar region, and described clinical manifestations closely simulating those presented here. Again, in 1942, he<sup>3</sup> reported three cases with block. One in the lumbar, one the dorsal, and one the cervical regions. Spurling and Bradford<sup>4</sup> described two cases, both at the fourth lumbar interspace, and a third case with obstruction due partially to protruded intervertebral disk and partially to arachnoid adhesions. Bunts,<sup>5,6</sup> using thoriatist myelography, reported one case with complete block at the fourth lumbar interspace and, using lipiodol, two more cases of block in the region of the third lumbar interspace. Another case is described in the records of the Massachusetts General Hospital<sup>7</sup> in which a block was encountered at the fourth lumbar interspace.

In our patients, the lesion occurred at the interspace of L-3 in one case, L-4 in four cases, and L-5 in three cases. The age incidence varied between 28 and 62. Three patients were in the third decade, two in the fourth, two in the fifth, one in the sixth, and one in the seventh decades.

The duration of symptoms varied from three weeks to 30 years. In most of the cases, it is interesting to note that there was a long period of prodromal symptomatology culminating in a short, rapidly progressing period of incapacity just before entry into the hospital. In none of these patients was there a history of sufficiently severe single injury to be of associated importance to the patient.

*History* The main complaints reported were pain, weakness, sensory disturbances and sphincter disorders. In three of the patients, twitching of the muscle of the legs was reported.

Pain was present in all patients. It was always the symptom of longest duration, usually beginning in the back and subsequently involving the legs. In all but one patient, it involved both legs. Usually, there was a long antecedent history of intermittent back pain for a period varying from seven months to 30 years, and a short period of three days to two months rapidly progressive bilateral leg pain, always of a severe nature.

Weakness of the legs was also a common complaint, being reported as such in five of the patients. It was sometimes difficult for the patient to evaluate weakness because of the pain. All but two patients were confined to bed at the time of hospital admission. In all but one case (Case 7) the weakness was a manifestation of the acute phase usually occurring a few days to a few weeks before admission.

Disturbances of sensation were reported in all cases but one (Case 3), and were, again, manifestations of the acute phase except in two cases (Cases 5 and 7). Usually the disturbance in sensation was described as numbness but the terms "prickling," "coldness," and "tingling" were commonly used. These disturbances of sensation were reported in one leg in four cases, the saddle area and both legs in two cases, and only the saddle area in one case.

Disturbances of elimination were reported in all cases. This complaint was always a manifestation of the acute phase being present for as long as two months in only two cases. It was nearly always of rapid onset, occasionally being preceded by a few days of increasing difficulty in voiding or increasing constipation. Complete retention of urine was reported in three cases and of urine and feces in one case. Marked difficulty in voiding was present in two cases, and difficulty in voiding plus constipation in two cases.

*Physical Examination* In all cases, there was evidence of weakness, atrophy, or poor muscle tone. This was not universally so extensive as might be expected, probably because of the relatively short duration of the acute phase of symptoms. Also, weakness was usually somewhat difficult to evaluate because nearly all of these people were in acute pain at the time of examination and, therefore, often restricted their effort. Atrophy of the glutei, thigh, or calf muscles was reported in four cases, and weakness and poor muscle tone in the same areas in the remaining four cases. The motor impairment was reported to be bilateral in four cases and unilateral in four cases. All but two patients were confined to bed.

Sensory disturbances were present in all cases. These changes varied considerably in extent and location but were universally bilateral. Disturbed sensation in the saddle area was common being present in five cases. This varied from dysesthesia to complete anesthesia, with trophic ulceration in one patient (Case 7). In two patients, sensory disturbances were reported as high as L-1 (Case 2), and D-10 (Case 4). In one of these patients (Case 2),

the lesion was found to be at L-3, and extensive arachnoiditis was encountered on opening the dura. In the remaining patients, sensory changes involved variously L-4 to S-5. Three of the patients with lesions at L-4 had portions of the L-4 dermatome involved. The greatest change, however, involved L-5, or below, in all cases.

The reflexes were altered in all cases. In five cases, the involvement was bilateral and in the remaining three unilateral. Alteration was uniformly present in the ankle jerks and, additionally, in the knee jerk in five cases. There were no cases of a single reflex being altered. In all cases, either both ankle jerks or a knee jerk and ankle jerk were impaired or absent. Those patients with pathology at L-3 and L-4 showed bilateral involvement in three cases and unilateral involvement in two cases. Of these, the knee jerk was impaired in all but one case. When the extrusion was at L-5, the involvement was bilateral in two cases and unilateral in one case, and the knee jerk was impaired in only one case.

Tidal drainage of the bladder was necessary in five patients, both before and after operation. Ability to urinate spontaneously returned in from nine days to five weeks, averaging two weeks. All patients with lesions at L-5 had complete retention while, of those with higher lesions, only two of five showed complete urinary sphincter involvement. The remaining three manifested varying degrees of difficulty in voiding.

Examination of the back was not well recorded in some instances, probably due to the acuteness of the patient's condition on entry. Tenderness was reported in four cases, spasm or limitation of movement in four cases, and no mention was made in one. Similarly, sciatic tenderness or sciatic stretch-tests were not well recorded, probably for the same reasons, although limitation in straight leg-raising was reported in five cases.

Roentgenograms of the back were taken in all cases—in one case elsewhere, but these films were reviewed by a member of the staff and reported to show nothing of significance. In two patients, a list was reported. In five patients, narrowing of an interspace was present, but in one of these (Case 2), the narrowing was not at the site of the proven lesion. Hypertrophic changes were reported in two patients (ages 62 and 56).

Spinal fluid protein determinations were made in six of the eight patients. The levels varied from 60 to 630 mg per cent. The highest figure represents fluid taken from below the lesion (Case 2), and cisternal fluid on this same patient was 25 mg per cent. In all other cases, the fluid was taken from above the lesion. In Case 8, a few red blood cells were reported present in the fluid.

Myelography was undertaken in all cases. In one instance this was done by cisternal puncture (Case 2), in the remaining cases by lumbar puncture. In all but one case (Case 2) pantopaque was used. In that one case, lipiodol was used. In all instances, complete, or nearly complete, block was encountered at the site designated. It was felt that this examination was a

good indication of the degree of obstruction because at body temperature, pantopaque has a low viscosity and flows readily. In one instance (Case 7), abnormalities were seen in two interspaces (L-4 and L-5) and at operation, an extruded nucleus pulposus was found at L-5 and a protruded intervertebral disk at L-4. There were no untoward reactions to myelography. The myelograms are shown in PLATE I.

*Operative Findings* The early patients were all explored with a preoperative diagnosis of cauda equina tumor. Subsequently, the correct diagnosis was suspected and in the last three was the primary preoperative diagnosis. Recently, however, one patient with a very similar clinical picture was explored with the same preoperative diagnosis but was found to have metastatic carcinoma in the upper sacral segment.

The operative findings were similar in all cases. Extruded nuclei pulposi severely compressing the dural sac were encountered and removed. The dura was opened in the first five cases. No mention was made as to the condition of the intrathecal contents other than they were "elevated to a marked degree" in two cases. In the remaining three cases (Cases 1, 2 and 5) thickening of the arachnoid, matting of the cauda equina, and adhesions were prominently present. In two of these cases (Cases 2 and 5) this was present to the extent that obstruction remained after removal of the extruded nucleus pulposus. Spinal fusion was done in three cases (Cases 1, 2 and 3).

*Sequelae* All patients were relieved of their pain postoperatively, and were ambulatory and voiding spontaneously on discharge from the hospital. Stay in the hospital after operation varied from 17 to 77 days, the average being 36 days. The longer hospitalizations were required for the patients who had spinal fusions. The average stay without fusion was 30 days. Two of the patients with fusions convalesced at home.

Follow-up varied from 2 to 16 months. One patient did not return. Three were operated upon within three months, and two of these had a two-month check-up. One patient (Case 1) had fairly extensive residual difficulty eight months after operation. She had weakness of her left foot, requiring use of a cane. There was also some vulvar anesthesia. Two others had a slight limp two months after operation (Cases 6 and 8). The remainder had no complaints when last seen. Two were reported working at their usual occupation, and one was simply reported asymptomatic.

#### CONCLUSIONS

The clinical similarity between herniated nucleus pulposus and early cauda equina tumors is generally well-recognized. The more advanced manifestations of neoplastic disease are, however, too often considered to be pathognomonic. The patients here reported suggest that herniated nucleus pulposus must be strongly considered even in the presence of advanced cauda equina compression. Herniated nucleus pulposus represents indeed in our experience, even a more common cause of such compressive manifestations than tumor. The differentiation between these two entities pre-

operatively is often impossible. The history and examination may present identical findings. All variations, up to complete block, may occur on lumbar puncture in both instances. Only the roentgenologic findings may be of differential aid. A narrowed interspace corresponding to a level of block at myelography should strongly suggest displaced intervertebral disk.

Another factor of possible importance in discogenic disease presented in these patients, is the presence of associated intrathecal inflammatory processes in the form of localized arachnoiditis. It was a very prominent manifestation in three of the five cases in which the dura was opened, and is possibly present to some degree in most of the cases. Some credence to this postulate might be taken from the universally increased spinal fluid protein encountered. A process of this type could possibly offer some explanation to such findings as sensory and motor changes corresponding to a level above the site of herniation as described in many of these patients. Further evidence of its possible importance was encountered in a recent case in which the patient developed rapidly progressing sensory changes, motor weakness, and sphincter involvement two weeks after removal of an uncomplicated displaced intervertebral disk. Repeat myelography demonstrated a complete block at the site of the operative removal instead of the original small defect. Reexploration four weeks after the original operation revealed no extradural pathology, but on opening the dura, an extensive localized arachnoiditis completely agglutinating the caudal filaments together was encountered. The symptoms and findings described disappeared during the next few weeks.

These patients may serve, also, to illustrate a possible danger in delaying operation for displaced intervertebral disk either because of faulty diagnosis or election. Nearly all had evidence of long preexisting discogenic disease yet the diagnosis was not made until all had evidence of extensive cauda equina compression. They were, thereby, subjected to extensively prolonged hospitalization and convalescence, and to the real possibility of crippling neurologic residuum. In view of the fact that many of these patients had minimal complaints prior to the acute episode culminating in cauda equina compression, it seems possible that any patient with discogenic disease might potentially suffer a similar fate. We feel this to be an argument in favor of myelography, certainly in equivocal cases and have used it routinely for two years.

#### SUMMARY

1 Eight cases of cauda equina compression due to herniated nucleus pulposus are presented. These cases are proven by myelography and operation.

2 This pathologic process was encountered at L-3 in one case, L-4 in four cases, and L-5 in three cases.

3 There is considerable similarity in the symptom complex presented by these patients. Their main complaints were pain in the back and both legs, numbness in the saddle area and/or both legs, weakness, and sphincter

disturbances In most cases, there is usually a long antecedent history of back pain followed by an acute episode of rapid progression of the above symptoms

4 The physical findings were also quite similar in all patients The predominant findings were weakness or atrophy in the gluteal region or both legs, sensory changes in both legs, multiple reflex changes and sphincter abnormalities

5 Narrowed interspace, determined roentgenologically, was frequently present, and of differential diagnostic importance when found

6 Increased spinal fluid protein was the rule

7 Myelography showed complete or nearly complete subarachnoid block in all cases

8 The presence of marked subarachnoid inflammatory processes was demonstrated, and its possible importance in this condition discussed

9 The difficulty in differentiating this clinical entity from cauda equina tumor preoperatively is apparent

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# LUMBOSACRAL ROENTGENOGRAMS OF 450 CONSECUTIVE APPLICANTS FOR HEAVY WORK

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ON SEVERAL OCCASIONS the authors have sought information on the subject of just what one might expect to encounter in the roentgenograms of a group of so-called normal lumbosacral spines, and have noted a marked scarcity of information in the literature on this subject. The question has been raised as to what is normal in regard to slight deviations from the perfect anatomic specimen and, here again, there is little in the literature relating to this. A great deal has been written about abnormalities (anomalies, injuries, and diseases) found in roentgenograms of patients with symptoms, but few observations have been made concerning roentgenograms of people with no complaints.

It has been the privilege of the authors to study the roentgenograms of a series (consecutive) of lumbosacral spines in men applying for work, for the most part heavy labor, at a large industrial plant\*. The results of this study were interesting as to the amount of gross abnormalities found and also the large number of cases showing slighter variations from the average normal. Because of the very high percentage of variation from the normal in these men who said they had no backache at the time they were seen or previously, it has seemed worth while to the authors to report this series.

It is of interest that the reason for taking routine low back roentgenograms of these patients was the industrial plant's previous unsatisfactory experience with litigation involving injuries to the lower back. In the year preceding starting the routine lumbosacral roentgenologic examinations, the industrial plant (a mine) had received several large adverse legal judgments in low back cases in which the allegedly injured individual had unquestionable previous pathology in some part of his lumbosacral spine. While no definite opinion can be expressed as yet, it appears that this type of litigation against the mining company is going to be greatly reduced since the introduction of the routine low back roentgenologic examinations, a saving which will far more than offset the cost of taking the roentgenograms.

The roentgenograms taken were of consecutive men applying for work,

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which was for the most part heavy labor. It had been hoped originally to make the series 1,000 cases, but the study was interrupted by the enlistment into the Army of two of the authors. It is felt, however, that 450 represents a significant number.

The views taken were flat anteroposterior and lateral views, each 14 x 17 inches, centering over the lumbosacral joint, but usually extending from the 11th thoracic vertebra to the coccyx. Stereoscopic, localized lateral, oblique or angled anteroposterior views were not made because of the additional expense.

TABLE I  
ANALYSIS OF ROENTGENOGRAMS OF 450 CONSECUTIVE LUMBOSACRAL  
SPINES IN APPLICANTS FOR HEAVY WORK

Pathology		Number of Cases	Per Cent
Hypertrophic changes	Severe	37	8
	Mild	59	13
	Total	96	21
Old compression fractures		22	5
Spondylolisthesis		14	3
Sacro iliac arthritis	Severe	8	2
	Mild	21	5
	Total	29	7
Transitional vertebrae—with anomalous joint (unilateral 17 and bilateral 16)		33	8
Transitional vertebrae—with no anomalous joint (unilateral 8 and bilateral 5)		13	3
Total		16	11
Structural scoliosis		6	1
Increased lumbar lordosis		8	2
Lumbar ribs		39	9
Six lumbar vertebrae		8	2
Spina bifida occulta		29	6
Other miscellaneous anomalies		8	2
Osteoporosis		3	1
Foreign body (metal in soft tissue)		2	0.5
Wedging of lower thoracic or upper lumbar vertebrae	Severe	42	9
	Mild	108	24
	Total	150	33
Narrowing of lumbosacral interspace, posteriorly	Severe	103	23
	Mild	140	31
	Total	243	54
CASES WITH SOME TYPE OF PATHOLOGY		389	86
CASES WITH PATHOLOGY EXCLUDING MILD LUMBOSACRAL NARROWING AND WEDGING OF THORACOLUMBAR VERTEBRAL		249	55
CASES WITH MULTIPLE PATHOLOGY		222	49
CASES REJECTED FOR WORK (SEVERE PATHOLOGY)		68	15
ADDITIONAL CASES WITH SEVERE PATHOLOGY		37	8

Facet defects, pedicle defects, and other conditions were undoubtedly overlooked in this series because additional views were not available. The authors feel this is unfortunate but unavoidable and had additional views been taken more pathology would have been found in all probability, and the scientific value of this paper enhanced. This report is presented with



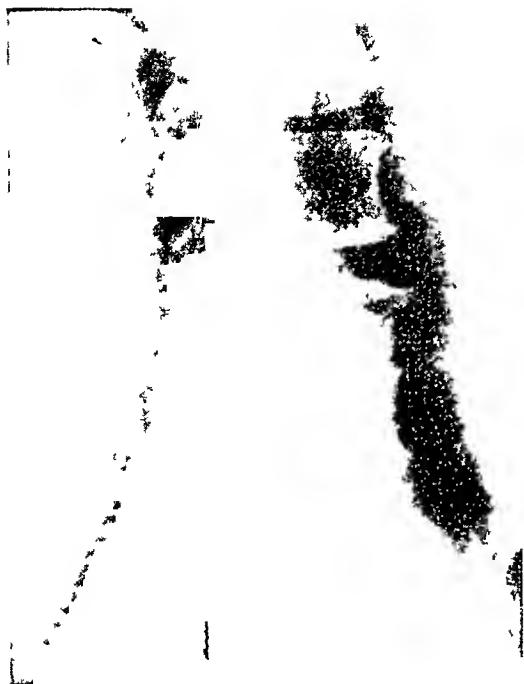


FIG 1—Hypertrophic arthritis of the lower lumbar spine. Note proliferative changes on the anterior margins of the vertebrae



FIG 2—Spondylolisthesis. Note pedicle defects with forward displacement of the fifth lumbar vertebra on the sacrum



FIG 3—Sacralization of the fifth lumbar vertebra. Note the anomalous articulations between the transitional vertebra and the sacrum



FIG 4—Old symmetrical wedging of the lower thoracic and upper lumbar vertebrae. This is usually due to an adolescent vertebral osteochondritis or epiphysitis

the foregoing facts in mind and for what it is worth based on the views available. The films themselves were in some instances good rather than perfect, but if the films were definitely at all unsatisfactory retakes were made. The area covered was from the 11th thoracic vertebra to the lower sacrum.

The analysis of the series will be found in Table I. The pathologic conditions have been broken down rather minutely, and it will be noted that the only grouped cases are "other miscellaneous anomalies," which contain only eight cases. With this exception, every case is accounted for in a definite place. Table I is, for the most part, self-explanatory, and only a few comments seem indicated.

The types of pathology really group themselves into two categories. The first, consisting of the most serious types, includes hypertrophic changes (Fig 1), old compression fractures, spondylolisthesis (Fig 2), sacro-iliac arthritis, transitional vertebrae (lumbarized 1st sacral segment or sacralized 5th lumbar segment) with anomalous transverse processes (Fig 3), and structural scoliosis.

The second group contains the conditions which are for the most part not so serious. This group includes increased lumbar lordosis, lumbar ribs, osteoporosis, foreign bodies, transitional vertebrae with no anomalous joint, anterior wedging of the body or bodies of the lower thoracic or upper lumbar vertebrae, and narrowing of the lumbosacral intervertebral space, posteriorly or generalized. The latter two conditions are worthy of special comment.

The old anterior wedging of the body of one or more upper lumbar or lower thoracic vertebrae is probably not often productive of symptoms (Fig 4). It is of great medicolegal importance, however, for often roentgenograms are taken after an injury has been received which might produce a compression fracture, and a wedging noted. In these cases it is sometimes very difficult to be absolutely sure about when the injury was received, and if the case goes to litigation some medical witness may often be found who will testify it is recent. A preemployment roentgenogram will definitely settle this. The very high incidence of old wedging in our series (33 per cent) should add weight to the belief that symmetrical wedgings are of little or no clinical significance. It has been suggested that most of them are due to a vertebral epiphysitis or osteochondritis of adolescence.

The importance of narrowing of the lumbosacral interspace (and intervertebral disk) is the subject of some controversy. Symmetrical marked narrowing accompanies a transitional vertebra, and in these cases is part of the anomaly. The cases classed as severe narrowing (subluxation) are those in which there was very marked posterior narrowing of the joint space with backward displacement of the 5th lumbar vertebra on the sacrum (Fig 5), and another group with marked symmetrical or posterior narrowing accompanied by sclerosis of the vertebral bodies in the areas closely adjacent

to the joint (marginal sclerosis) The cases classed as mild narrowing in this series are those with only a little narrowing and with little or no backward displacement of the 5th lumbar vertebra With a quite definite narrowing of the lumbosacral joint space both anteriorly and posteriorly, or with marginal sclerosis of the adjoining vertebral bodies, they were not included in the mild group Recently, a growing number of orthopedic surgeons (including the authors of this paper) have felt that lumbosacral subluxation is a common cause of low back pain The fact that over one-half (54 per cent) of the cases in this series had posterior narrowing of the lumbosacral joint is not inconsistent with the above view, but it certainly indicates that the 10-cent-



FIG 5—Posterior subluxation of the fifth lumbar vertebra on the sacrum. Note the marked downward and backward displacement of the fifth lumbar vertebra.



FIG 6—Multiple pathologic conditions. Traumatic wedging of the twelfth thoracic and first lumbar vertebrae, a small loose piece of bone on the anterosuperior margin of the fourth lumbar vertebra, and posterior lumbosacral subluxation—all in the same individual.

genogram alone is of little help in evaluating these cases as far as excessive joint motion is concerned It is felt that mild or moderate posterior narrowing of the lumbosacral joint is normal, or at least a variant of the normal, since it is present in at least some degree in over one-half the men in this series

It is interesting that in so large a series there were no cases of tuberculosis, osteomyelitis, or cases with a previous fusion operation This would lead one to think individuals with these conditions either feel they are permanently disabled or are really so disabled

The analysis of gross pathology is interesting in that altogether 86 per cent

of cases showed something that could be described. If the cases of mild wedging of vertebral bodies and mild lumbosacral narrowing are excluded (but still including those with lumbosacral narrowing accompanied with posterior displacement of the vertebra above, those with sclerosis of the vertebral margins, and those with transitional vertebrae), the percentage of pathology is 31 per cent. Of the original group, 49 per cent showed multiple pathology (Fig 6), although many of these included lumbosacral narrowing or wedging of the upper lumbar or lower thoracic vertebrae.

Of the 450 cases, 15 per cent were rejected for work. The authors felt from the standpoint of the patients' roentgenograms they were very liberal in allowing such a high percentage to go to work, for many of those allowed to work showed considerable pathology, and a definite 8 per cent (additional to the 15 per cent) showed very marked pathology which might lead to trouble. Thus, there was the almost astonishing figure of 23 per cent of cases in which there were marked pathologic findings.

COMMENT—This series of cases brings up a very real and important problem as to what pathologic conditions render a man unemployable in heavy industry, and the authors are not prepared to answer this question. It is probably an individual problem in each case. Such things as an old compression fracture with marked hypertrophic changes, or a spondylolisthesis, are potentially dangerous from the employer's standpoint as possibly productive of symptoms, compensation or litigation. The value of preemployment low back roentgenograms is certainly made clear in this series, and it is hoped more of these may be made and reported in the literature, by others.

#### SUMMARY

A series is reported of 450 consecutive lumbosacral spine roentgenograms taken in applicants for work in a heavy industry.

Table I summarizes the pathologic changes found—and a very high incidence was present. Thirty-one per cent of the cases showed significant pathologic changes, and in 15 per cent the pathology was severe enough to render them unemployable in heavy industry, in the authors' opinion.

The conditions present are analyzed and evaluated, and the great value of preemployment roentgenologic examination is pointed out.

# COMPARATIVE VALUES OF VARIOUS METHODS OF RESUSCITATION\*

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IN ANY ATTEMPT at resuscitation following asphyxia, there are two important and fundamental factors which may determine the outcome. The first is the prompt employment of the resuscitation procedure. The second is the inherent value or effectiveness of the procedure itself. Of the first factor, all investigators are agreed upon the necessity for the prompt application of the resuscitation procedure. Concerning the second factor, however, there are as many opinions as there are different methods of resuscitation.

It is important to keep in mind that respiration and circulation are intimately related and cannot act independently of each other for any length of time. Therefore, resuscitation procedures not only may have to be directed towards an adequate pulmonary ventilation but also towards an adequate circulation to carry the oxygen to the heart and brain. In asphyxia, however, the first efforts should be directed towards pulmonary ventilation.

In the minds of the laity as well as most of the profession there is still the belief that manual artificial respiration is the "procedure of choice" in asphyxia. Loughheed, Janes and Hall<sup>1</sup> in an excellent experimental investigation came to the conclusion that "as a result of our experiments we consider that prompt, adequate and prolonged artificial respiration is the fundamental treatment for drowned, asphyxiated or electrocuted persons."

Henderson and Turner<sup>2</sup> believe that manual artificial respiration is more effective than mechanical resuscitation. Coilylos<sup>3</sup> was of the opinion that the mechanical suck-and-blow resuscitator was superior to manual artificial respiration. Thus, the value of various resuscitative methods has been, and still is, a controversial subject.

Because of the conflicting opinions and the existing confusion, we have reviewed this problem and have attempted to clarify it experimentally by a critical comparison of the methods in ordinary usage.

These methods fall into two general groups: (1) Manual, and (2) mechanical. Our principal objectives were to compare the manual method with the mechanical methods and to determine the comparative values of the various methods.

In this investigation dogs were used throughout, and since a modified Sylvester method gave the greatest amount of pulmonary ventilation, only this method of manual artificial respiration was used.

All methods produce pulmonary ventilation in one of the following ways,

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\* Read before the New York Surgical Society, April 12, 1944

(1) Positive inhalation and release produced by positive insufflation of the lungs, (2) deflation, produced by external compression or by negative suction and (3) a combination of inhalation and deflation produced by positive insufflation alternating with negative suction deflation

The manual method produces an active exhalation or deflation of the lungs. Inhalation is dependent upon muscle tone and the elastic recoil of the chest wall. The mechanical apparatuses are chiefly inhalators, insufflators and resuscitators. The insufflators produce an active inflation of the lungs. Deflation depends upon the elastic recoil of the lungs and chest wall. The resuscitators employ active insufflation alternating with suction deflation of the lungs and have either a volume or a pressure control. Whether it be a pump automatically operated or the anesthetic bag manually compressed, no apparatus, however simple, is devoid of the danger of alveolar rupture unless it has a pressure control feature and only those apparatuses with pressure control should be used. Simplicity does not always mean safety.

In comparing methods or mechanical apparatuses, it is desirable to have all conditions of the tests as nearly constant as can be, and the test itself should eliminate as many extraneous factors as possible. For this reason we have used the "asphyxial resuscitation test" as the method of comparison.

During the course of previous experiments in resuscitation we observed an interesting phenomenon which, to our knowledge had not been previously described. We<sup>4</sup> described and called this "the phenomenon of asphyxial resuscitation." Briefly, it consists in the ability to regularly restore the circulation and respiration in advanced asphyxia, *without the benefit of oxygen*, by means of inflation alternating with suction deflation of the lungs, using an inert or asphyxiating gas (nitrogen, helium).

Paradoxical as it may seem, it is possible to resuscitate an animal in asphyxia from the inhalation of an inert gas (when respirations have stopped and the blood pressure is at or rapidly approaching zero) by the rhythmic inflation and deflation of the lungs, using the same gas which had just previously been used to produce the asphyxia. Resuscitation by this method is also possible in asphyxia produced by mechanical obstruction of the air passages.

Later experiments<sup>5</sup> showed this phenomenon to be a reflex from nerve endings in the lungs, carried by way of the vagi to the medullary centers. Adrian<sup>6</sup> has demonstrated in the lung the presence of nerve endings called "stretch receptors" which give rise to measurable action currents. They are unaffected by anesthetics or by a lack of oxygen and even cardiac cessation and circulatory failure have no immediate effect upon them. Their function is to signal the volume of the lung at each movement. One set of the end-organs is active only on inspiration or inflation of the lungs. Another totally different set is stimulated by suction deflation of the lungs. This latter set of end-organs is not stimulated by the normal expiratory or respiratory movements and there is no evidence of their activity in moderate dyspnea.

Forceful deflation of the lungs by external compression of the thorax in some animals is not enough to stimulate these end-organs. However, they do react quite readily to suction deflation. This provides a rather complete answer to the question of why suction deflation is necessary in resuscitation.

We have used the "asphyxial resuscitation test" because it completely eliminates the stimulating effect of oxygen and places the entire burden of resuscitation upon the method or apparatus itself. The test is made as follows. The animal (dog) is anesthetized with intraperitoneal nembutal. An endotracheal tube with occlusion cuff is inserted into the trachea, and the cuff is inflated. Under air-tight precautions a cannula is inserted into the pleural space. The femoral artery is cannulized. These two cannulae and the endotracheal tube are connected to separate recording mercury manometers which register upon a single revolving drum. The animal is now allowed to inhale, through the endotracheal tube, pure nitrogen gas, until asphyxia has progressed to a "critical point," in the third stage of asphyxia. This critical point is beyond the place where spontaneous resuscitation could occur and is determined by respiratory cessation, a rapidly falling blood pressure, and a slowing with irregularity of the heart. When this "critical point" is reached, the method or apparatus to be tested is put into operation, however, the endotracheal tube is still connected with the pure nitrogen gas. The method is applied until resuscitation occurs or the animal dies. Resuscitation is recognized by a sustained rise in the blood pressure and the return of spontaneous respiration. After the first spontaneous respiration has occurred, the endotracheal tube is disconnected from the nitrogen and is exposed to the atmosphere and all resuscitative measures are discontinued.

Asphyxia has been divided into four stages. Initial apnea, dyspnea, cessation of respiration or terminal apnea, and arrest of heart. Although it has been convenient to consider that the total duration of acute asphyxia is approximately four minutes, with each stage occupying about a minute, the actual duration of each stage and the total time may vary.

In evaluating resuscitation methods it is necessary to consider the possibility of spontaneous resuscitation and at what point it may occur in asphyxia. It was demonstrated by Coryllos<sup>3</sup> that when asphyxia of submersion is interrupted before the middle of the third stage, spontaneous resuscitation is possible, he considered that in obstructive asphyxia "removal of the obstructing agent before the end of the third phase is followed as a rule by spontaneous resuscitation." Since he considered his stages to occupy about a minute, this would place the critical point for spontaneous recovery less than 30 seconds from the time respiration ceased in the case of submersion asphyxia and less than 45 seconds from the cessation of respiration in the case of obstruction asphyxia. Lougheed, Janes and Hall,<sup>1</sup> in a study of asphyxia by drowning and tracheal obstruction, have found that after cessation of respiration there is a critical point at which the heart beat ceases to be expulsive. In general, the point at which respiration ceased and the point at which the asphyxial procedure was stopped could not exceed

18 seconds if spontaneous recovery were to take place. If this period was extended even a very few seconds longer, resuscitation would be impossible.

We have shown that asphyxial resuscitation (using an inert gas) is possible far beyond the point in asphyxia where spontaneous recovery could take place. Generally, we have started asphyxial resuscitation well beyond the 45-second point of the third stage of asphyxia at a variable "critical point" where the heart action becomes altered and irregular. The length of time which may elapse between respiratory cessation and the successful application of asphyxial resuscitation varies in each experiment, the longest interval was two and three-quarter minutes. In the usual resuscitation experiment, the circulation recovers first followed by the recovery of respiration. Even though the circulation has recovered, the method is usually continued in action until spontaneous respiration has taken place, although this is not always necessary.

TABLE I  
EFFICIENCY OF DIFFERENT RESUSCITATIVE PROCEDURES

<i>Nitrogen</i>			
	Success	Failure	Per Cent of Success
1 Manual artificial respiration	1	6	15
2 Rhythmic inflation	2	10	17
3 Rhythmic suction	1	4	20
4 Resuscitation (rhythmic inflation and suction)	30	5	85

Comparing various methods of resuscitation<sup>8</sup> by this test (Table I) we found manual artificial respiration was successful in 15 per cent, inflation-and-release was successful in 17 per cent, suction deflation-and-release was successful in 20 per cent, combined inflation alternating with suction deflation was successful in 85 per cent.

TABLE II  
EFFICIENCY OF DIFFERENT RESUSCITATIVE PROCEDURES

<i>Oxygen</i>			
	Success	Failure	Per Cent of Success
1 Manual artificial respiration	6	5	55
2 Rhythmic inflation	7	2	78
3 Rhythmic suction	4	1	80
4 Resuscitation (rhythmic inflation and suction)	21	1	95

When the tests were repeated, using, however, oxygen (100 per cent) instead of the nitrogen during the period of resuscitation (Table II), we found manual artificial respiration was successful in 55 per cent, inflation-and-release was successful in 78 per cent, suction deflation-and-release was successful in 80 per cent, combined inflation alternating with suction deflation was successful in 95 per cent.

Interpretation of these results shows the marked superiority of mechanical over manual methods of resuscitation. Further analysis of these results shows the importance of using suction deflation in resuscitation procedures.



since suction alone was more successful than either manual artificial respiration or inflation and release. These results also show the superiority of mechanical resuscitators using inflation alternating with suction deflation, over all other methods.

### CONCLUSIONS

Since the prompt application of the resuscitative procedure is of prime importance and since manual artificial respiration is usually the only method at hand, it is suggested that in asphyxia, manual artificial respiration be immediately applied and continued until a mechanical resuscitator using safe pressure can be substituted. The importance of using suction deflation in resuscitation has been shown. Those resuscitators employing both insufflation as well as negative suction deflation are the most efficient of the mechanical apparatuses and gave the largest percentage of successful resuscitations. It is recognized that all methods of resuscitation are dependent upon patent air passages.

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# STUDIES ON SURGICAL CONVALESCENCE<sup>1</sup>

## I—SOURCES OF NITROGEN LOSS POSTGASTRECTOMY AND EFFECT OF HIGH AMINO-ACID AND HIGH CALORIC INTAKE ON CONVALESCENCE

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IN A PRELIMINARY COMMUNICATION on this subject<sup>1</sup> it was reported that patients convalescing from gastrectomy, when fed with a high caloric and high amino-acid diet (nutramigen) were able to maintain a consistently positive nitrogen balance throughout the postoperative period, to register a rise in body weight, and to achieve an early return of strength and a significantly shortened convalescence. This picture was in striking contrast with that of a similar group of postoperative patients under the classical postoperative ward regimen, who had a consistently negative nitrogen balance, a loss of body weight, a longer period of postoperative debility, and a more prolonged stay in bed.

The present series may be considered a continuation and further development of the previous work. Of the 19 cases reported here, eight (Group A) were on routine ward regimen, eight (Group B) were fed high caloric and high amino-acid mixture, and an intermediate group of three (Group A') were fed, but not in enough quantities to maintain nitrogen equilibrium. Seven in A, six in B, and all the three in A' had complete nitrogen balance studies for from seven to 12 days. Three patients each in A and B had ergographic tests performed.

### EXPERIMENTAL CONSIDERATIONS

The conditions under which the present study was carried out were, in the main, similar to those in the first series. The following modifications were made in the light of additional experience.

(1) *Types of Cases*—Unlike the former series which eliminated cases with complications, except wound infections, the present series was a random one in which cases with as well as without complications were included.

(2) *Use of the Abbott-Rawson† (AR) Tube*—In the present work the

\* The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and New York University and read in abstract form before the Committee on Convalescence and Rehabilitation of the National Research Council, November 16, 1943.

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‡ The Abbott-Rawson tube is manufactured by George P. Pilling & Son, Arch and 23rd Streets, Philadelphia, Pa.

AR tube, which was devised by Abbott-Rawson<sup>2</sup> for a similar purpose but which has been modified by leaving out the metal bucket, was used instead of the modified Miller-Abbott used in the former series. The larger bore of the AR tube facilitated feeding and the lighter weight of the jejunal portion of the tube minimized the possibility of erosion of the tissues at the anastomosis. The construction and use of the tube is shown in Figure 1.

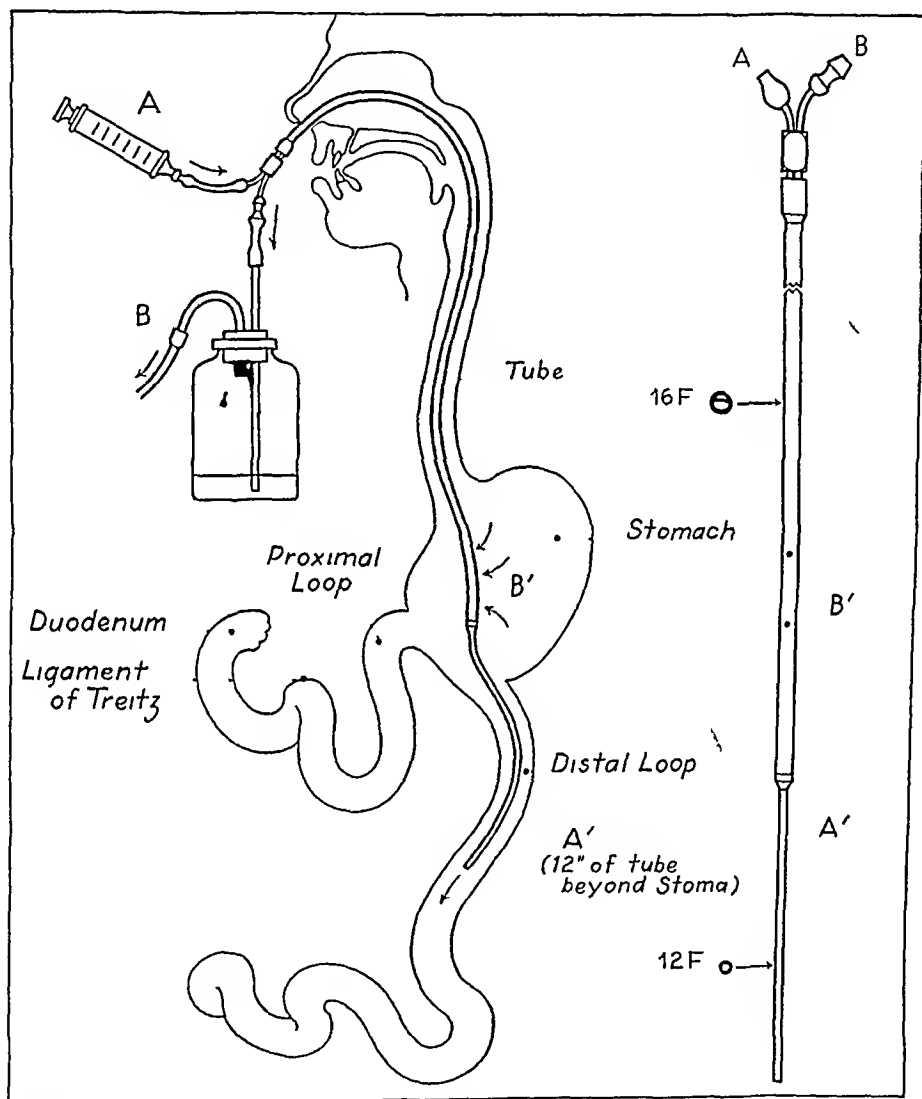


FIG. 1—A line drawing showing the use of the Abbott-Rawson tube in gastrectomy cases.

Having been tested for patency and autoclaved, the tube was passed into the stomach through one of the nares the night before the operation. The next morning, one hour preoperatively, the stomach was emptied by suction through both lumens of the tube. During the operation and at that stage of anastomosis between the stump of the stomach and the jejunum when the row of hemostatic sutures had reached halfway round the anterior aspect of the stoma, the anastomosis was interrupted in order to pass the feeding end of the AR tube into the jejunum. This was done under aseptic pre-

cautions The assistant grasped the distal loop of the jejunum for a distance of 12 inches, holding it up between the fingers of both hands The surgeon inserted a pair of long sponge-forceps through the anastomotic opening into the lumen of the stomach and, by locating the tip of the tube with his free hand from the exterior of the stomach wall, he picked it up with the sponge-forceps The forceps, with the tip of the tube in the jaws, were withdrawn from the stomach and inserted into the distal loop of the jejunum until the junction of the gastric and jejunal portions of the tube lay just proximal to the anastomosis The assistant, by palpating through the jejunal wall then located the tip of the tube and held it in place while the surgeon disengaged and withdrew the forceps, which were then discarded The operative work was then resumed

Postoperatively, for from four to six days, as indicated, Wangensteen suction was maintained through the suction lumen of the AR tube, thus keeping the stomach empty

The fluid and caloric intakes were governed by the Collier and Maddock<sup>3</sup> principles

(3) *The Caloric Intake*—In A the caloric intakes were all subbasal, consisting solely of the infusions of dextrose in the first five to six days and of the sugar in tea and the peptonized milk given in subsequent days In A' the intake was almost basal, while in B it was never under 2,000 daily (50 calories per kilogram body-weight), consisting in the first five to six days of amigen and dextrimaltose, and in the balance of convalescence usually also of the fat present in nutramigen

(4) *Use of Digestate Mixtures*—In the former series nutramigen was used exclusively Nutramigen contains the casein digestate, amigen, reinforced with dextrimaltose, starch, fat, salts and yeast powder It yields 47 calories and 0.027 Gm of nitrogen per Gm The salts contribute to the mineral balance and the yeast powder presumably furnishes the vitamins This mixture has been used in pediatrics as the sole nutriment for infants and babies for over five years<sup>4</sup> Its composition, however, makes it difficult to make a stable instillable suspension, and during the first four or five days postoperatively, when it may become necessary to use a high nitrogenous feeding in small volume, nutramigen is unwieldy

Amigen which is more soluble, more easily maintained in suspension, and contains much more nitrogen, is, therefore, indispensable It yields 34 cal per Gm, and contains 12 per cent nitrogen Aside from sodium chloride, no other constituents are present The nitrogen requirements are first calculated (0.6 Gm N per the Kg body-weight) and then dextrimaltose was added in sufficient amounts to make up the requisite caloric intake Recently, it has been our practice in many cases to use amigen-dextrimaltose mixtures during the first five to six postoperative days, adding nutramigen after the AR tube was removed It was thought desirable to do this in order not to deprive the patients of essential fatty acids for too long a period of time This use of varying amounts of amigen and dextrimaltose also permits a

greater elasticity in the adjustment of nitrogen and caloric intakes, a problem which is sometimes difficult when either powder is used exclusively

Amigen and dextrimaltose mixtures, because of their high solubility, and lack of "body," may be made with any volume of water. With nutramigen, which is less soluble, the use of 1 cc of water per Gm of the substance makes an easily instillable mixture. When amigen and nutramigen are used in the same formula, the use of 1.2 to 1.5 cc of water per Gm of nutramigen usually was enough to take the amigen into solution as well.

The powdered ingredients were weighed and mixed together in a mixing bowl. The calculated volume of hot water was then measured and poured into the powder, stirring all the time. After thorough mixing, the mixture was poured into milk bottles and placed in the refrigerator at approximately 40° F.

(5) *The Nitrogen Intake*—In A, the only nitrogen intake during the first days postoperatively was in the form of blood or plasma transfusions. Other than this, during the first five days it was almost nil. From the sixth day on, small gradually increasing amounts of peptonized milk constituted the entire nitrogen intake. At about the tenth day, more substantial food was added, the nitrogen content of which was calculated from the dietitian's chart.

The patients in B derived their nitrogen intakes from the amigen or nutramigen given, the usual nitrogen intake being in the neighborhood of from 0.4 to 0.6 Gm per Kg body-weight, the latter amount exceeding the intake of a high protein diet by 1.5 to 2.2 times. The patients in A' were also fed either amigen or nutramigen, or both, but in quantities not sufficient to maintain caloric or nitrogen balance.

(6) *The Feeding Schedule*—It may be helpful to set forth in some detail the feeding regimen as now practiced in the feeding cases. For the first 6 to 12 hours postoperatively, infusions of 5 per cent amigen in physiologic saline and dextrose solutions were given. After that, for the cases in which the surgeon was sure of the flawlessness of his technic, feeding was started, beginning from 30 cc per hour for the first four to six hours to 50 cc every hour for the remainder of the first postoperative day. The volume was increased from 60 to 90 cc on the second day and from 90 to 100 cc thereafter. The following is a sample schedule.

R. B., Age 48, Weight 63 Kg						
P O Day	By Tube—Gm		N Intake		Caloric Intake	
			Gm	N Gm/Kg		
		By Vein—Gm	8.8	0.14	1040	
		Plasma 250 cc				
		Amigen 50				
1	0	Glucose 200				
	Amigen 250	Amigen 100				
2	D M 500	Glucose 150	42	0.67	3815	
3	Same	Amigen 50				
		Glucose 150	36	0.57	3560	
4 to 11	Amigen 350					
	D M 600	0	36	0.56	3420	

It will appear from the above schedule that, during the first day, the caloric and nitrogen intake, when only intravenous infusions were given the first six to twelve hours, followed by 30 to 50 cc of oral feeding every hour, as restricted by the restriction in fluid intake and that intravenous feeding barely made up caloric and nitrogen requirements. On the second day the tube feeding alone yielded a sufficient caloric and nitrogen intake, but was insufficient for fluid replacement, and, therefore, intravenous medication had to be given. On the third day, the intravenous fluid supply was reduced to one liter and after the fourth day this was dispensed with, the entire caloric, nitrogen and fluid requirements having been supplied through the tube.

It will be recalled that, in our first series of cases, it was possible to dispense with intravenous fluid therapy altogether, thereby saving the patient a great deal of discomfort. To do this, however, meant increasing the volume fed by tube to from 100 to 150 cc an hour, starting after the first 12 hours. This large volume of feeding for the first postoperative day would not be easily acceptable to the average surgeon. For this reason, and for the reason that the patients under this more conservative regimen did not seem to fare any worse, the above compromise feeding schedule is recommended. In the ultimate analysis, a rigid program will only be rejected by most of the surgical profession and, thus, defeat its own purpose.

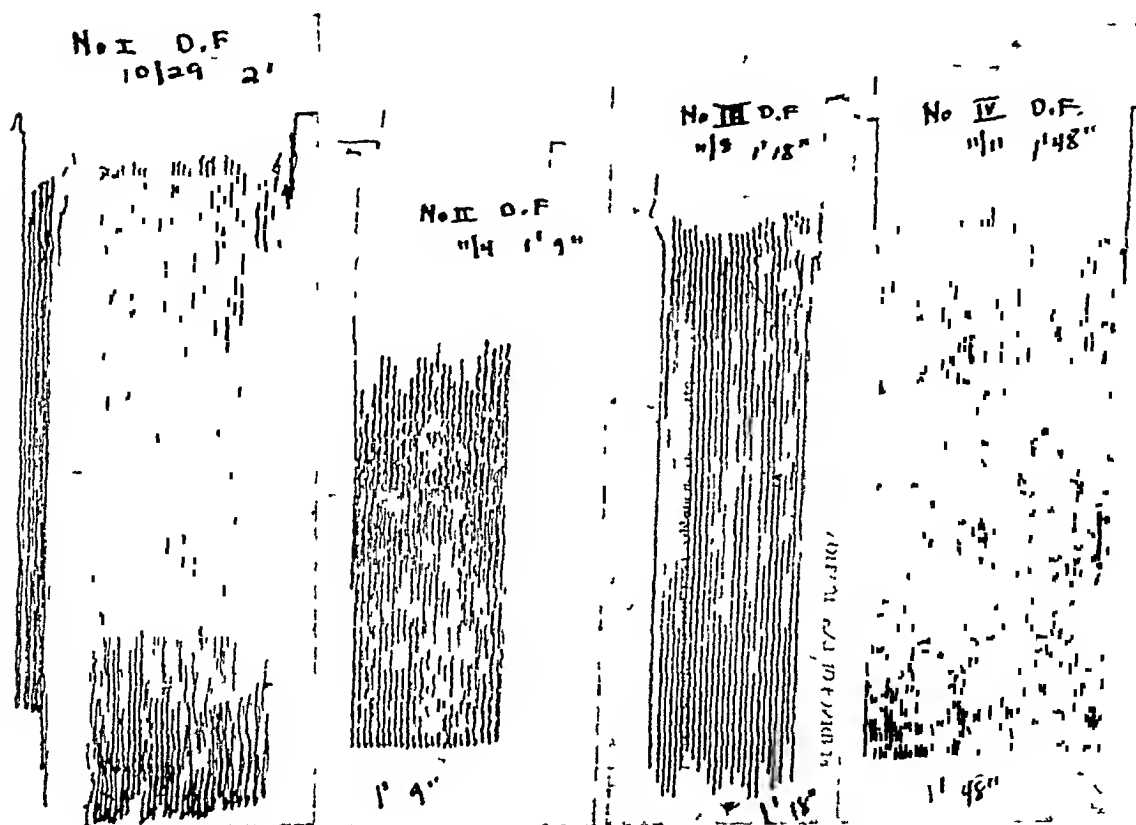
(7) *Vitamin Intake*—Throughout convalescence, beginning from the first postoperative day, the following complement of vitamins was given intramuscularly: Thiamine chloride, 50 mg, ascorbic acid, 100 mg, niacin, 50 mg. After the fifth day, these were given by mouth.

(8) *Management of Distention and Diarrhea*—The incidence of early distention in this series is unusually small in all groups. When distention persists after the first 48 hours, small doses of prostigmin in combination with the Harris drip rapidly reduced it. In not one of the eight full feeding cases in this series was it necessary to discontinue feeding as a result of distention.

In our former series when nutramigen was fed, diarrhea sometimes ensued after the first two or three days of feeding. This was perhaps due to the presence of fat in the nutramigen. In the present series, using an amigen-dextrimaltose feeding mixture, whatever tendency to diarrhea was present was controlled by the routine administration of amphojel, 4 cc four times daily, by the tube the first two days and by mouth thereafter. Occasionally this was supplemented by small doses of paregoric.

(9) *Ergography*—The bedside ergograph, the construction and use of which has been described in a separate paper,<sup>5</sup> was used to test the endurance of the patients preoperatively and periodically, postoperatively in three patients in A—D F, Table V, F Mc, Table VII, and M K, Table VI; three in B—R B, Table XVI, C N, Table XIV, and A V, Table XIII. This was an attempt to study objectively whether there was asthenia in the control cases and early return of the patients' strength in the feeding cases—possibilities strongly suggested by our first series.

A short description of the test may not be amiss. The upper extremity was placed on the board of the ergograph so that the forearm was free. Through a cable and a set of pulleys, a weight of either 3, 5, or 10 Kg, depending upon the robustness of the patient, was lifted and lowered, the excursions being registered on a moving drum. These efforts were spaced every three seconds, and at the point when the patient felt painful fatigue in the arm, the lifting was discontinued. This was the end-point. The length of the entire test from the beginning of the first to the end of the last excursion is expressed in seconds and is called the ergograph-time (E. T.)



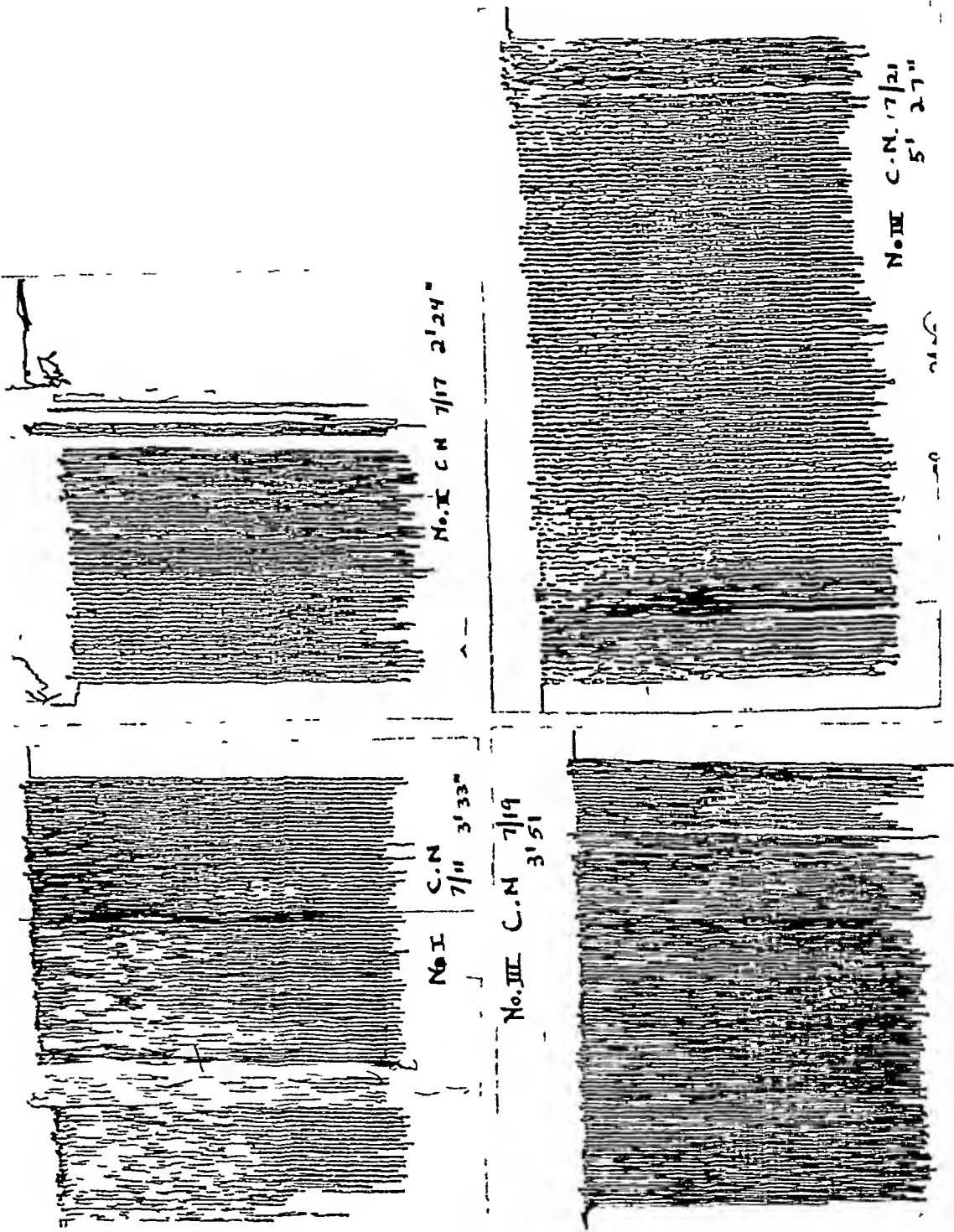
GRAPH 1—The ergograph time of patient D. F. (Table V) under postgastrectomy ward regimen. Note that the initial ergograph time in Panel I was 2', that Panel II on the fourth postoperative day showed a depression to 1'9", and that in Panels III, and IV, taken respectively, on the 8th and 11th postoperative days, the ergograph time had not reached the initial value.

Graphs 1 and 2 show the ergographs of a control compared with a feeding case.

(10) *Collection and Care of Specimens*—The urine and feces were collected according to the directions given in the preliminary report. The chemical methods used were also the same as those used in that series.

#### ANALYSIS OF THE TABLES

There are presented for analysis, 16 individual tables (Tables I to XVI) each recording the nitrogen intake and output, the nitrogen balance, the cumulative nitrogen status, the plasma proteins, the hematocrit, the weight, and the immediate postoperative history of the patient. For purposes of simplification, the columns on fluid output, and volume of gastric drainage



GRAPH II—The ergograph time for C. N. (Table XIV) under high-alimentation regimen. Note that there was a depression of the ergograph time in Panel II, on the 6th postoperative day, but that in Panel III on the 8th postoperative day the initial value had been exceeded.



have been omitted. These figures differed very little from those of the previous series except that in one case (M K, Table VI), in whom there was frank postoperative hemorrhage, and in two cases (A S, Table VIII), and W C, Table IX, in whom hemorrhage was suspected, the volume of drainage resulting from the gastric suction was unusually large.

TABLE I  
C W MALI 58—CARCINOMA PYLORUS  
Nitrogen Output

Date	Daily N Intake Gm	Total N Intake Gm	Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
Jan 12													
13-14	0	2 8	24 66	2 5	1 44	28 60	-25 72	-25 72	6 3	41	54 81		Gastrectomy 500 cc W B
11-15	0												
15-16	2 8												
16-17	2 85	9 42	21 45	1 3	1 44	24 19	-13 39	-39 19	5 67	39		53 45	
17-18	3 8												
18-19	2 77												
19-20	3 8	3 8	15 50		48	15 98	-12 18	-50 37					
20-21	6 8	6 8	7 6		48	8 16	-0 84	-52 21				52 96	
21-22	6 8	6 8	7 16		48	7 64	-0 36	-52 57					
22-23	6 8	6 8	7 6		48	8 08	-1 28	-53 85					
23-24	7 15	14 30	19 17		96	20 13	-4 83	-58 68				51 82	
24-25	7 15												
26												50	
30												49 55	Out of bed—17th day
Total	50 72		103 4		5 76	112 78							Disch to sanitarium—(19th day)
Avg	4 23		8 62		48	9 39							

TABLE II  
A D MALE 59—DUODENAL ULCER  
Nitrogen Output

Date	Daily N Intake Gm	Total N Intake Gm	Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
March 5													
6-7	17 5	24 75	31 88	6 55	41	38 87	-14 12	-14 12	6 12	42	62 25		Gastrectomy 500 cc W B and amigen
7-8	7 25												
8-9	0	85	27 85	11 57	44	39 86	-39 01	-53 13	6 71	43			Temp 102 8°
9-10	85												
10-11	1 32	6 78	36 48	6 38	66	43 53	-36 74	-89 87				Temp 102 2°	Temp 102 6°
11-12	1 82												
12-13	3 64												
13-14	3 11	10 71	33 88		66	34 54	-23 83	-113 7				Temp 102 4°	Temp 101 8°
14-15	3 4												
15-16	4 2												
Avg						13 68							Temp 102
25													Temp normal
31													Out of bed (19th day)
Total		43 09	130 09			2 2	156 8						Discharged to sanitarium (25th day)
Avg		4 31	13 01			22 15 68							

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TABLE III  
T S, MALE 64—DUODENAL ULCER

Date	Daily N Intake Gm	Total N Intake Gm	Nitrogen Output			Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
			Urinary N Gm	Gastric N Gm	Fecal N Gm								
March 23												55.5	Gastrectomy 500 cc W B
23-24	2.8	2.8	23.12	9.06	1.0	33.18	-30.38						
24-25	0												Fever 101°
25-26	0			10.3									Fever
26-27	0	0	36.99		1.5	48.79	-48.79	-79.17	4.52	24		52.1	Fever
27-28	0												Fever to 10th day
28-29	4.3												
29-30	4.2	13.7	29.04		1.5	30.54	-16.84	-96.01					
30-31	5.2								4.39	30			
April 1												49.05	
11												48.3	Out of bed (18th day)
13													Discharged (20th day)
Total		16.5	89.15		4.0	98.81							
Avg		2.1	11.14		5	12.35							

TABLE IV  
I B, MALE 34—DUODENAL ULCER

Date	Daily N Intake Gm	Total N Intake Gm	Nitrogen Output			Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
			Urinary N Gm	Gastric N Gm	Fecal N Gm								
April 1									6.25	42	64.32		Gastrectomy 500 cc W B
1-2	2.8	2.8	12.28	9.09	1.00	22.37	-19.47						
2-3	0												Fever 102°, chills
3-4	0												Mucopurulent
4-5	0	0	24.2	9.29	1.5	34.99	-34.99	-54.46					expectoration, X-rays negative
5-6	0												Fever between 101-103° to 12th
6-7	6.8			3.8					6.04				P O day
7-8	6.2	19.45	38.4		1.5	43.7	-24.25	-78.71					
8-9	6.45												
11												60.05	
24													Out of bed (23rd day)
May 11									5.99	37			Discharged (39th day)
Total		22.25	74.88		4.0	101.06							
Avg		2.78	9.36		5	12.63							

TABLE V  
D I MALE 55—CARCINOMA PYLORUS  
Nitrogen Output

Date	Daily N Intake Gm	Total N Intake Gm	Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm	N Balance Gm	Cum N Status Gm	P P Gm % or A/G Hem	Wt Kg	Remarks
Oct 30									3 31/1 92 32	59	Erg T —120 sec Gastrectomy — 2 units plasma
30-31	2 4										
Nov 31-1	2 4	4 8	19 03	2 89	82	22 74	-17 94				
1-2	2 4								5 17 42		Erg T 69" Temp rise in PM to 102° Febrile Febrile
2-3	0	2 4	20 46	6 52	1 23	28 21	-25 81	-43 75	5 11		Wound infection Erg T —78" Wound still dis- charging
3-4	0										
4-5	2 2										
5-6	2 2	8 6	17 23		1 8	19 03	-10 43	-54 18			
6-7	4 2										
7-8	4 2	8 4	20 82		1 2	22 02	-13 62	-67 80	5 09 39		
8-9	4 2										
9-10						9 2					Temp normal Erg T —108"
13										50	
17											Out of bed weak (18th day) Discharged (20th day)
19											
Total	24 2	77 54	5 05		92						
Avg	2 42	7 75	5		9 2						

TABLE VI  
M R MALE 55—DUODENAL ULCER  
Nitrogen Output

Date	Daily N Intake Gm	Total N Intake Gm	Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm	N Balance Gm	Cum N Status Gm	P P Gm % Hem	Wt Kg	Remarks
Dec 15									5 62 41	68	Erg T —398" Gastrectomy 500 cc W B
16-17	14 8										Gastric hemor- rhage 500 cc W B
17-18	12	32 6	51 86	13 71	2 2	67 77	-35 17				Temp 104°, slightly icteric Erg T —299" Febrile
18-19	5 8										
19-20	14 8										
20-21	2 2	19 2	69 6	14 93	1 27	85 80	-66 6	-101 77			
21-22	2 2								5 62 30		
22-23	4 2										
23-24	4 2	14 6	41 2		1 27	57 07	-42 47	-144 84			Temp normal
24-25	6 2										
28										61 81	Erg T —300" Out of bed (13th day)
Total		66 4	162 66		4 74	210 64					
Avg		7 4	18 07		53	23 40					

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TABLE VII  
F MC, MALE, 46—DUODENAL ULCER  
Nitrogen Output

Date	Daily N Intake Gm	Total N Intake Gm	Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
May 7									5	48	33	52 5	Erg T—114" Gastrectomy, May 8
8-9	2 4	4 8	22 42	3 38	3 51	29 31	-24 71		5	09	30	49 09	2 units plasma Temp 102 6°
9-10	2 4												Febrile
10-11	0												Febrile
11-12	0												Febrile
12-13	0	0	27 32	2 07	3 51	32 90	-32 94	-57 65					Febrile
13-14	0	0											Febrile
14-15	1 2	7 2	21 14		3 51	27 65	20 45	-78 10	5	81	32		Erg T—42" Temp normal
14-15	2 2												
16-17	3 5												
17-18	3 8												
18-19	4 4	12 6	27 65		3 51	31 16	-18 56	-96 66	5	53	33	47 95	Erg T—84"
19-20	4 4												Out of bed (17th day)
25													Discharged to Sanit (20th day)
28												45 91	
Total		24 6	101 53		14 04	121 02							
Avg		2 05	8 63		1 17	12 1							

TABLE VIII  
A S MALT, 28—DUODENAL ULCER  
Nitrogen Output

Date	Daily N Intake Gm	Total N Intake Gm	Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
May 26												41 37	Gastrectomy, May 27, 500 cc W B
27-28	2 8	27 6	41 93	14 19	1 53	57 65	-30 05						Cyanosis
28-29	12 8												Cyanosis
29-30	12												Cyanosis
30-31	12 5												Cyanosis
June 31-1	10 5	41 0	37 44	23 29	1 53	62 26	-21 26	-51 31					Cyanosis
1-2	18												unexplained Cyanosis
2-3	10												disappeared
3-4	12	32 5	34 5		1 53	36 03	-30 53	-55 84				37	Cyanosis
4-5	8 5												disappeared
5-6													
6-7													
7-8													
10													Out of bed June 10
Total		10 11	113 42		4 59	155 94							
Avg		11 2	14 91		51	17 33							

TABLE IX

W C MALE 30—DUODENAL ULCER

## Nitrogen Output

Date	Daily N Intake Gm	Total N Intake Gm	Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
March 12									6	17	45	57 27	Gastrectomy 500 cc W B
12-13	10 8	51 82	49 06	54 94	1 77	105 77	-53 95						Fever—104° Pulm atelectasis L L L Febrile
13-14	21 75												
14-15	19 27												
15-16	19 27	59 29	59 57	13 25	1 77	74 59	-15 30	-49 25	6	60	30	52 41	Febrile
16-17	20 75												
17-18	22 75												
18-19	18 75	64 25	58 49		1 77	60 26	+ 3 99	-45 26	6	43	27	53 22	Fever still 101 8 98 8° Out of bed (13th day) Discharged— (19th day)
19-20	22 75												
20-21	22 75												
25													
31													
Total		175 36	167 11		5 31	240 62							
Avg		19 37	18 57		59	26 74							

TABLE X

J B MALE 49—DUODENAL ULCER

## Nitrogen Output

Date	Daily N Intake Gm	Total N Intake Gm	Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
Mar 1									5	85	40	42 72	Gastrectomy
1- 2	12	20 05	22 29	1 35	66	24 3	- 2 01						
2- 3	8 05												
3- 4	8 54												
4- 5	10 64	19 18	29 32	96	66	30 94	-10 76	-12 77	5	99	33		
5- 6	6 55	19 97	25 29	48	99	26 76	- 6 31	-19 08				41 81	Fever—102 6°
6- 7	7 74												
7- 8	5 68												
8- 9	5 47	19 73	32 88	✓	99	33 81	-14 08	-33 16				41 59	Fever
9-10	6 63												
10-11	7 63												
Avg									5	21	36		Fever
													Wound abscess—
													13th day — fever
													for 6 days after
													Bed sores
April 8													Out of bed
													(37th day)
Total		79 13	109 28		3 3	116							Discharged
													(42nd day)
Avg		7 91	10 98		33	11 6							

TABLE XI  
G H, MALE 39—CARCINOMA PYLORUS  
Nitrogen Output

Date	Daily N Intake Gm	Total N Intake Gm	Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
Feb 1									6	36	60	64 8	Gastrectomy
2-3	26 65		19 73	71	1 69	22 13	+4 52	+4 52					
3-4	27 9		16 36	1 26	1 69	19 32	+8 59	+13 11					
4-5	25 1		13 31	1 82	1 69	17 32	+7 78	+20 89					
5-6	22 08		18 76	97	1 69	21 41	+ 67	+21 56	6	5	54	65 1	Fever 108° L U atelectasis with pneumonitis (Xray confirmed)
6-7	27 9		15 10	1 31	1 69	18 1	+9 8	+31 36					
7-8	23 4		18 65	46	1 69	20 8	+2 6	+33 96	6	36	50		
8-9	23 4		14 94	07	1 69	16 69	+6 71	+40 67					Temp normal
9-10	23 4		23 87		1 69	25 56	-2 16	+38 51					
10-11	23 4		17 49		1 69	19 18	+4 22	+42 73				66 54	
11-12	23 4		22 96		1 69	24 65	-1 25	+41 48					
12-13	23 4		16 53		1 69	18 22	+5 18	+46 66					
13-14	23 4		21 30		1 69	22 99	+ 41	+47 07				67	Out of bed (13th day)
15									6	36	49		
16													Discharged (15th day)
Total	293 43		219 00	21 9	20 28	231 26							
Avg	24 45		18 25	8 22	1 69	20 53							

TABLE XII  
P R, MALE 48—DUODENAL ULCER  
Nitrogen Output

Date	Daily N Intake Gm	Total N Intake Gm	Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
Feb 26									5	7	33	75	Gastrectomy
27-28	42 8	74 8	25 11	5 14	2 34	32 59	+10 21	+10 21					
28-31	32												
March													
1-2	32	64	35 94	17 12	3 51	56 57	+ 1 43	+17 64	6	46	33		
2-3	32												
3-4	32												
4-5	32	96	46 85	22 76	3 51	73 12	+22 88	+40 2					
5-6	32												
6-7	32											77 27	
8	32												Out of bed (8th day)
9	32											79 54	
10	32												
Total	362 8		107 9		9 36	162 28							Discharged (11th day)
Avg	32 97		15 41		1 34	23 18							

TABLE XIII

A V MALE 55—DUODENAL ULCER

Date	Daily N Intake Gm	Total N Intake Gm	Nitrogen Output			Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
			Urinary N Gm	Gastric N Gm	Fecal N Gm								
July 18									6	26	41	67	Erg T —270" Gastrectomy
19-20	11	35	38 2	1 63 11 91	1	40 88	- 5 88	- 5 88	6	19	36		Unexplained fever—106° Unexplained fever—104° Erg T —189" Temp normal
20-21	21												
21-22	30												
22-23	6	66	42 64		1 5	55 55	+10 45	+ 4 57					Erg T —327"
23-24	30	87	32 23		1 5	33 73	+53 27	+57 84	6	07	35		Erg T —327"
24-25	27												
25-26	30												
26-27	30	100	24 67		1 5	25 87	+45 13	+102 97	6	66	33	71 85	Out of bed (9th day) Erg T —348" Discharged (11th day)
27-28	30												
28-29	35												
30	35												
Aug 1													
Total		288	137 94		5 5	156 03							
Avg		26 2	12 54		5	14 18							

TABLE XIV

C N MALE 59—CARCINOMA PYLORUS

Date	Daily N Intake Gm	Total N Intake Gm	Nitrogen Output			Total N Output Gm	N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
			Urinary N Gm	Gastric N Gm	Fecal N Gm								
July 10									6	25	38	54	Erg T —213" Gastrectomy
11-12	18	60	37 36	4 52	1 56	43 46	+16 54	+16 54	5	75	37		Fever—104° Pul- monary path ? Fever—101 6° Temp normal Erg T —144"
12-13	18												
13-14	24												
14-15	24	85	29 1	5 04	1 56	35 7	+49 3	+65 84	5	43		56	Erg T —231" Out of bed (10th day)
15-16	31												
16-17	30												
17-18	30	90	71 21		1 56	72 77	+17 23	+83 07	5	34			Erg T —327" Discharged (13th day)
18-19	30												
19-20	30												
20-21	30	90	38 91		1 56	35 97	+54 03	+137 10	5	71	38	59 3	
21-22	30												
22-23	30												
Total		325	176 58		18 92	187 9							
Avg		27 08	14 72		52	15 66							

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TABLE XV

E B, MALE, 35—DUODENAL ULCER

Date	Daily N Intake Gm	Total N Intake Gm	Nitrogen Output				N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
			Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm							
Dec 1									5	24	32	36 82	Gastrectomy 3 units plasma
1-2	8 4	68 4	19 07	22 529	7 08	38 68	+29 72	+19 72					Fever—103° • Purulent bron- chitis? Fever—101 8° Temp normal
2-3	36												
3-4	24												
4-5	24	72 00	22 07	10 145	7 08	39 3	+32 7	+62 42	5 31	33			
5-6	24												
6-7	24												
7-8	24	72	21 23	18 3	7 08	46 61	+25 39	+87 81	4 77				
8-9	24												
9-10	24												
10-11	24	48	18 88		4 72	23 60	+24 94	+112 75					Out of bed (10th day) Discharged (17th day)
11-12	24												
18													
Total		260 4	71 25		25 96	148 19							
Avg		25 68	6 48		2 36	13 47							

TABLE XVI

R B MALE 48—DUODENAL ULCER

Date	Daily N Intake Gm	Total N Intake Gm	Nitrogen Output				N Balance Gm	Cum N Status Gm	P Gm	P %	Hem	Wt Kg	Remarks
			Urinary N Gm	Gastric N Gm	Fecal N Gm	Total N Output Gm							
Nov 20									6	14	43	60 23	Erg T—54"
22-23	38 8	80 8	34 18	3 97	1 14	40 29	+40 51	+40 51					Nov 22— Gastrectomy— 500 cc W B
23-24	42												
24-25	36	108	67 18	5 84	3 21	76 23	+31 77	+72 28				63	Erg T—110"
25-26	36												
26-27	36												
27-28	36	108	55 64		3 21	58 85	+48 15	+120 43					Erg T—120"
28-29	36												
29-30	36												
Dec 30-1	36	72	44 25		1 14	46 39	+24 61	+145 04					Erg T—160" Out of bed (10 days) Discharged (15th day)
1-2	36												
3													
8												64 55	
Total		368 8	201 25		8 7	218 7							
Avg		36 88	20 13		87	21 87							



TABLE XVII  
MASTER TABLE SHOWING NITROGEN BALANCE STUDIES IN 16 CASES OF GASTRECTOMY

Group Name	Sex	Age	Orig Body Weight Kg	Diagnosis	No Days Under N	Average Daily N Intake Gm	Daily N Intake per Wt Kg	Average Daily Fecal Nitrogen Gm	Loss or Gain of Nitrogen Gm	Loss or Gain of Body Wt Kg	Days of Return Strength	Days in Bed	Remarks
A	G W	58	54.81	Ca-pyl	13	4.23	08	48	-58.68	-5.26		17*	Uneventful
	A D	59	62.5	D U	10	4.31	07	22	-113.7	-4.78		19	Pulmonary atelectasis with low-grade fever to 11th day
	T S	64	55.5	D U	8	2.1	04	5	-96.01	-7.3		18	Temp rise from 2nd day to 10th Mild cold No other complications
	P B	34	64.32	G U	8	2.78	04	5	-78.71	-4.27		23	Fever 102.4° F from 9th to 12th days Wound infection (abscess) on 21st day
	D I	55	59	Ca pyl	10	2.42	04	5	-67.86	-9	Not on 12th day	18	Pyrexia—102° F from 5th to 8th days p o wound infection discovered 7th day, wound separation 26th day
	M. K	55	68	D U	9	7.4	11	53	-148.84	-6.19	Not on 12th day	13	Hematemesis (500 cc) on 2nd p o day Temp 104° F on 4th day to normal in three days
	I Mc	46	52.5	D. U	12	2.05	04	1.17	-96.66	-6.59	Not on 12th day	17	Unexplained pyrexia (103° F) on first to sixth days
	N G	M	70.5	Ca pyl			06			-7.8		24	P O pneumonia on 8th day, fever to 12th day Wound separation 12th day
A'	A S	M	28	41.37 D U	9	11.2	27	51	-55.84	-4.37		18 6	Unexplained cyanosis from 1st to 6th p o days
	W C	M	30	57.27 D U	9	19.37	18	59	-45.26	-4.05		13	Fever from 2nd to 6th p o day (104° F) Pulmonary atelectasis
	J B	M	49	42.72 D U	10	7.91	19	33	-33.16	-1.7		37	Fever 102.6° F from 8th day Low wound infection and peritoneal abscess found on reoperation, 13th day Bedsores
B	G H	M	39	64.8 Ca pyl	12	24.45	42	1.69	+47.07	+2.2		13	P O atelectasis (X ray confirmed) 3rd p o day temp 103° F falling to normal in three days
	P R	M	48	75 D U	7	32.97	44	1.34	+68.05	+4.54		8	Uneventful
	A V	M	55	67 G U	11	26.2	48	5	+102.97	+4.85	Between 5th and 9th days	9	Temperature 106° F on 3rd day—again 104° F on 4th day Normal thereafter
	N C	M	59	54 Ca pyl	12	27.08	6	52	+137.10	+5.3	Between 4th and 8th days	10	Fever 104° F on 3rd p o day—probable pulmonary pathology Fever lasting two days
	E B	F	35	36.82 D U	11	23.68	61	2.36	+112.75	+5.85		10	Fever 103° F on 4th p o day—purulent bronchitis Temp normal on 5th day
	R B	M	48	60.23 D. U	10	36.88	6	87	+145.04	+4.32	Between 4th and 6th days	10	Uneventful
	A H	F	33	60 Ca-pyl		30	5			+4		10	Uneventful
	G S	F	75	55 Ca-pyl		24	44			+6		8	Uneventful
Average												9	

Table XVII is a master-table summarizing the findings in the three groups with relevant correlative calculations and with columns numbered for ready reference. In A, there was included an additional case (R G), in whom the nitrogen-balance study was not done, but in whom the weight-curve and the period of stay in bed were recorded. In B, there were also two such cases (A H and G S).

*The Nitrogen Intake*—Column 8, Table XVII, shows that in both A and A' the nitrogen intake was abnormally low, ranging from a minimum of 2.1 Gm per day (T S) to a high of 7.4 Gm (M K), most values being in the neighborhood of 2.0 to 4 Gm daily. The intake per kilogram body-weight ranged from 0.04 (T S, P G, D F, and F Mc) to 0.11 Gm (M K). In B, the intakes ranged from 2.4 (G S) to 3.7 Gm daily (R B), or from 0.39 (A V) to 6.5 Gm (E B) per Kg body-weight. These intakes are much higher than those obtained by high protein diets, and in a 70-Kg man would correspond to from about 750 to 1350 Gm of meat daily.

*Urinary Nitrogen*—In A and A', except for the cases in which melena occurred, the urinary nitrogen excretion was unusually low, ranging from 7 to 12 Gm as a daily average, except for G W (Table I), whose excretion rose to 15.5 Gm on the seventh day, without assignable cause, and for A D (Table II), whose excretion was 31.88 Gm for the first two days. There is, thus, in this and in our previous series, little evidence of a significant and sustained large loss of urinary nitrogen following such a major surgical insult as gastric resection. It must, however, be remembered that all these patients had undernutrition before they came to operation and were in practical starvation for several days following. The finding by Cuthbertson<sup>6</sup> that starved animals sustaining injuries do not lose the amount of nitrogen lost by previously normal animals, may explain this small loss encountered in our cases.

In the group with hemorrhage, or suspected hemorrhage, where the gastric nitrogen was unusually high, there was also a high urinary nitrogen excretion—14.9 Gm for A S (Table VIII), 18.17 for M K (Table VI), and 18.57 for W C (Table IX). Here the high urinary nitrogen may be explained on the basis of "alimentary azotemia," which has been reported by Chunn and Harkins,<sup>17</sup> and others, as accompanying gastro-intestinal hemorrhage.

In B, as may be expected from the high nitrogenous diet, the urinary output was generally considerably larger. E B (Table XV) was an exception, with an average excretion of only 6.48 Gm daily. However, she had suffered a large loss of weight before entry into the hospital, at which time her weight was only about 37 Kg. The other cases had average urinary nitrogen values of from 12.54 (A V, Table XIII) to 20.13 Gm (R B, Table XVI). These values do not differ much from the values of our first series of feeding cases.

*The Fecal Nitrogen*—In the total number of ten cases, in the Groups A and A', except for the three cases of postoperative hemorrhage, the fecal

excretion was inclined to be on the starvation level—mostly under 0.5 Gm daily. In only one case (F Mc, Table VII), did it consistently average over 1 Gm daily. In the three cases of actual or suspected hemorrhage, the fecal excretion was over 0.5 Gm, but under 1 Gm. In B, the excretion values were over 0.5 Gm daily in two cases, over 1 Gm in three cases, rising to over 2 Gm daily in one case. This is to be expected with the high nitrogen intake, although it falls below the average value of 10 per cent of the intake, as is assumed to be the case with the ingestion of natural food. This finding may indicate that preparations like amigen are more completely absorbed than natural food. These fecal nitrogen values accord with the findings in our previous series. Column 10, Table XVII, gives the average daily values for fecal nitrogen.

*Gastric Nitrogen*—The amount of nitrogen present in the Wangenstein suction varied from a fraction of 1 Gm daily to almost 10 Gm. It is possible that figures above this may point to a postoperative hemorrhage. In the one case in which there was frank postoperative hemorrhage (M K, Table VI) and in two in whom postoperative hemorrhage was suspected, this figure rose to as high as 23 Gm a day (M K, Table VI).

*The Total Nitrogen Output*—Although the urinary values were low in A and A', the additional nitrogen loss in the gastric suction tended to make up the total nitrogen values, so that the total nitrogen excretion was not far below accepted normal values—the lowest daily average being over 9 Gm (G W, Table I, and D F, Table V). However, only in the cases with detected or suspected hemorrhage was total nitrogen excretion much above normal accepted values (M K, Table VI, A S, Table VIII, and W C, Table IX).

In B, total nitrogen excretion was high as might be expected from the increased nitrogen intake.

*The Nitrogen Balance*—With the exception of one three-day period in the case of W C (Table IX), the nitrogen balance in A and A' was consistently negative in the two groups. In B with the exception of the first day, when the intake in some cases was deliberately restricted, the nitrogen balance was consistently positive throughout the feeding period. This nitrogen gain on the part of the body ran from a fraction of 1 Gm a day to as much as 55 Gm in a three-day period.

*The Cumulative Nitrogen Status and the Weight-Curve*—Columns 11 and 12 in Table I represent, respectively, the cumulative nitrogen status and the weights of the patients. The cases in A and A' all showed nitrogen deficits ranging from 35.55 (W C, Table IX), to 140.60 Gm (T S, Table III). These were associated with marked weight losses ranging from 1.7 Kg (J B, Table X) to 10.23 Kg (A D, Table II). In the cases in B, the nitrogen surplus ranged from 45.13 Gm (A V) to 145.04 Gm (R B), and the weight gains from 2.2 Kg (G H) to 6 Kg (G S). Theoretically, for every 32 Gm of nitrogen lost or gained by the body, there ought to be

a corresponding loss or gain of 1 Kg of weight. Unfortunately, for a better correlation, the weights were not taken simultaneously with the termination of the nitrogen balance studies. However, it can be seen from the figures in all three groups that, although there was no strict mathematical parallelism between the magnitude of nitrogen deficits and surpluses, large losses of nitrogen were associated with large losses in weight and large gains of nitrogen with large gains in weight.

*The Plasma Protein and Hematocrit Levels*—In the previous report it was stated that the general tendency of the plasma protein level was downward in the control group, and upward, or relatively stationary, in the following group. In the present group of six control cases, a downward tendency was discerned. In A' there seemed to be a suggestive rise. The picture was somewhat erratic in B, the trend being upward in three, stationary in one, and downward in two. Nor did there seem to be any consistent pattern to the hematocrit values except in the two cases with postoperative hemorrhage. In any event, the changes in the protein values downward or upward did not seem significant, and in the absence of blood volume determinations neither value is interpretable.

*Ergograph Time and Postoperative Asthenia*—Patients D, F (Table V), F, Mc (Table VII), and M, K (Table VI) in A and patients R, B, C, N, and A, V in B were tested with the bedside ergograph. The tests were performed one or two days before the operation and in the fourth, eighth day and twelfth day postoperatively. As may be seen from column 13 of Table XVII, both groups showed a depression of the ergograph time on the fourth postoperative day. In the cases in A the return to normal had not occurred on the twelfth postoperative day, while the three cases in B had exceeded their initial ergograph time in from the fifth to the ninth day postoperatively. Graphs 1 and 2, respectively, represent a control case (D, F, Table V), and a feeding case (C, N, Table XIV). The initial ergogram-time (E, T) in Panel I (Graph 1) was 120 seconds. The E, T in Panels II, III and V, respectively, 4, 8, and 11 days postoperatively are 69, 78, and 108 seconds. Thus, on the eleventh day, the endurance had not yet returned to the initial level. The initial E, T Panel I, Graph 2 two days preoperatively, was 213 seconds. The E, T in Panels II, III, and IV respectively, four days, six days, and eight days postoperative were 164, 231 and 327 seconds. Thus, while there was also a depression on the fourth postoperative day, on the sixth postoperative day the endurance had already surpassed the initial endurance. This seemed to correspond with the subjective feeling of asthenia, or lack of it, in these two groups.

*The Length of Stay in Bed*—As far as the authors are aware, the subject of when an operative patient should be allowed to get out of bed has never been examined critically and objectively. Offhand, two factors seem to enter into this consideration. The healing of the operative wound and postoperative asthenia. In the control cases, there would be a number expected to have

such malnutrition that the wound would not heal or would heal slowly. One case in our previous series and one in the present series showed this condition, culminating in wound dehiscence (J B). Thus, these two factors seem to play a role in the prolonged bed-stay of this group, sometimes one factor, sometimes the other, in the dominant rôle.

In the patients in the feeding group, in whom nutrition was supported by this type of rich feeding, the speed of wound healing would be expected to follow, at least, the norm demonstrated by the work of Howes, Sooy and Harvey,<sup>7</sup> and the maximal tensile strength of the healed wound would be in the neighborhood of 10 to 12 days. On the other hand, the ergograph-time had topped the initial reading in from the sixth to the eighth day. Thus, it appears that in the feeding group it is the speed of wound healing, rather than the postoperative asthena, which retards the patients' stay in bed. It will be seen from column 14 of Table XVII that the average number of days in bed is 19.25 days for A. Strictly considered, this average figure is too low, since M K (Table VI), the one patient with a stay in bed of 13 days, was fed for a period of ten days preoperatively, resulting in a gain of 3.3 Kg. This improvement of his preoperative nutritional state makes it necessary, in interest of strict comparison, to exclude him from the series. With this done, the average period of stay in bed would be 20.1 days. In the feeding group, on the contrary, the corresponding average of 9.5 days (column 14, Table XVII) in bed is higher than it should, theoretically, be. To allow patients convalescing from an operation of the magnitude of gastrectomy out of bed in eight days is a radical departure from surgical tradition, and usually involves a compromise in which two or three additional days are added to the period of recumbency. It may also be mentioned that the patients in B clamored to get up by about the seventh day, while those in A had to be encouraged to get up.

*Complications* — (Column 15, Table XVII) — The small series of 11 patients in A and A', and of eight in B, are too small to make any statistically significant analysis of the complications as affected by postoperative feeding or nonfeeding. There were three pulmonary complications in each group, but the recovery seemed to be considerably longer in A than in B. There were three wound infections in A and A', one wound separation, and one case of bedsores, while the cases in B were free from these complications. The case of bedsores is interesting in view of a recent work by some of the present authors<sup>8</sup> on the relationship between bedsores and protein nutrition. At the time the bedsores occurred, the plasma proteins of J B, (Table X) was 5.01 Gm per cent. Only two of the patients in A and A' may be said to have had an uneventful course in any way, while there were four uneventful cases in B.

In A, another complication was encountered, *i e*, a delayed type of disturbance of gastro-intestinal function occurring at about the sixth to ninth postoperative day in five of the eight cases. It manifested itself in the form

of abdominal distention, with vomiting and inability to take more than a small amount of liquid food at frequent intervals. Two factors may be evoked to explain this phenomenon (1) Edema about the stoma, and (2) deficient peristalsis, tone and absorptive faculty of the small intestine consequent to undernutrition. This did not occur in any of the cases in B.

*Disadvantages*—In the previous report, the principal disadvantage of this feeding regimen was said to be the taste of the feeding mixture. This still remains the main drawback. However, in the, rather extended experience we have had with the use of the mixture, it seems that most patients readily yield to persuasion and will continue taking it if they realize that it produces beneficial results. When the choice is left to the patient, whether to take feedings by mouth or by tube, the oral method is usually preferred.

**DISCUSSION AND COMMENTS**—Altogether, 24 patients convalescing from gastrectomy have been subjected to nitrogen balance studies in this and in the previous series. Three additional patients had only their weights and their length of stay in bed recorded. There was, thus, a total of 13 in the control group and 14 in the feeding group. In none of the patients in the control group, except in the cases with actual or suspected gastric hemorrhage, did there seem to be a loss of urinary nitrogen above that accepted as normal average. Cuthbertson<sup>6</sup> has shown a nitrogen loss to occur following trauma. Albright,<sup>9</sup> and Browne<sup>10</sup> have ingeniously integrated this with Selye's<sup>11</sup> "alarm reaction" and an hypersecretion of hormone "s" from the adrenal cortex preventing tissue anabolism. These workers have called this period of nitrogen loss the antianabolic period. If this phenomenon had occurred in our series, it certainly was not marked. However, as pointed out before, the previous state of undernutrition might have modified or altogether eliminated the antianabolic period.

In the feeding group, the early ability of the patients to achieve nitrogen balance as well as the consistent upward weight curve may be interpreted to mean that if an antianabolic period was present, it was correctable by high amino-acid feeding. This, again, is not in apparent conformity with Cuthbertson's and Browne's findings, but, again, the state of undernutrition of our patients may reconcile the divergence of these results.

It is also apparent that although the urinary excretion of nitrogen may be small in these cases, the addition of the nitrogen lost in the gastric suction may raise the total nitrogen output considerably above the amount prescribed as optimum protein requirements for the average person, namely, 90 Gm. of protein or 14.4 Gm. of nitrogen daily.

The level of nitrogen feeding attained in the patients in B, as has been pointed out elsewhere in this report, is much higher than that of a high protein diet. It is, roughly, two to three times the average amount of the total nitrogen loss. There may be said to be at least two justifications for giving such large doses of nitrogen. In the first place, it is not known just what specific amino-acids are required to replace the nitrogen loss, and this

increased alimentation may be considered an attempt to offer enough of an assortment of amino-acids in sufficient quantities so that the body can select what it needs under optimum conditions and reject the rest. Approximately 50 per cent of the bulk of amigen is composed of the ten essential amino-acids, 40 per cent being unessential amino-acids and the balance, moisture and ash. It is altogether unlikely that the proportions of the ten are ideal, and, it is highly probable that the unessential moiety is excessive. Therefore, an ideally economical utilization cannot be expected from such a mixture. The wonder is that it should be so well utilized that the total nitrogen excretion in B were not larger than they are. However, it is quite possible that a drastic reduction of the unessential moiety would make for a greater economy of utilization.

The second justification for the use of these large amounts of nitrogen is that all of these cases, except one, M K (Table VI), were in a state of undernutrition when they came to operation. This increased alimentation is, therefore, necessary not only adequately to make up the nitrogen loss during and after the operation, but also to replace the body tissues lost as a result of the preexisting undernutrition. The fact that some of these patients retained as much as 53 Gm of nitrogen in three days shows the need of the body to rebuild itself.

In this connection, Elman's<sup>12</sup> summary concluding a report on the oral use of amigen in surgical patients, may be worth while quoting. He stated "The amino-acids of hydrolyzed casein (amigen) have been administered directly into the gastro-intestinal tract in several types of surgical patients in order to spare the need for protein digestion. Absorption and utilization occurs under circumstances when whole protein is ineffective. The use of amigen also seems to permit the assimilation of much larger daily amounts of protein nourishment than seems possible when whole protein is given."

The tendency of the plasma protein level not to rise even after there is a considerable gain in body weight and a positive nitrogen balance for several days needs further study. Similar results have been obtained with post-operative patients by other workers (Aniel, *et al*,<sup>13</sup> Casten, Bodenheimer and Barcham,<sup>14</sup> and Meyer<sup>15</sup>), although in the case of the observations of these workers, no high amino-acid feedings had been given and the weight curve was not followed.

These experiments recall to mind a practice reported by Soviet surgeons of introducing milk, egg and sugar mixture into the intestines during celiotomy with marked, prompt benefit to the patients and a reduced mortality rate. There were, thus, two separate beneficial effects reported as resulting from the use of such feedings—one immediate and the other delayed. The feeding consisted of 400 cc milk, 20 cc sweet butter, 50 grams sugar, 2 eggs, and 50–70 cc distilled alcohol. Analysis shows that it would not yield more than 1500 calories, even if the alcohol was 95 per cent. There was a nitrogen content of about 8 Gm. The immediate beneficial effect is probably attributable

to the alcohol, since it is difficult to understand how the caloric and nitrogen intake could accomplish this. And since the caloric and nitrogen intakes are subbasal for even one day, it is also difficult to explain the delayed beneficial effects, unless two or three such feedings are given daily throughout convalescence.

#### SUMMARY AND CONCLUSIONS

In a further and larger series of patients undergoing gastrectomy for either peptic ulcer or carcinoma of the stomach, it was found that

(1) In the series under the classical ward regimen there was a consistent nitrogen deficit and loss of weight, and a prolonged stay in bed, confirming the preliminary results of our previous series. Objective eigography also showed postoperative asthenia, which had not disappeared even on the twelfth postoperative day.

(2) In the series fed with high caloric and high amino-acid mixtures, there was a consistent nitrogen surplus, a steady gain in weight and a stay in bed of less than one-half the control series. The eigograph showed an early return of endurance in from the fifth to the sixth postoperative day to above that of the initial reading.

(3) The principal source of nitrogen loss in postgastrectomy convalescence was the starvation postoperative regimen.

(4) Whether there was actually a larger excretion of urinary nitrogen in the patients in the control group over their preoperative level has not been determined.

(5) The nitrogen loss resulting from the gastric suction was considerable.

(6) The nitrogen loss, however, was correctable by feeding an easily assimilable high amino-acid mixture.

(7) Contrary to the impression gathered in the previous series, that there was a tendency of the plasma protein level to fall in the control cases and to rise during the feeding cases, in the present series there was no consistent tendency during the seven to twelve days during which the patients were under study.

(8) An hyperalimentation regimen, consisting of high caloric and high amino-acid feeding postoperatively, has been worked out, found practical, and is recommended in the routine case of gastrectomy in order to circumvent nitrogen loss, shorten convalescence, and prevent postoperative asthenia.

(9) While the complications in the feeding group are fewer and less severe than those in the control group, the present series is too small to lead to any statistically significant conclusions.

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# BRIEF COMMUNICATION

## THE CONSTRUCTION AND USE OF A BEDSIDE ERGOGRAPH\*

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IN THE COURSE of some studies on convalescence, it became desirable, objectively, to determine the strength and endurance curve of patients recovering from surgical operations. Since ergographs then available were all devised for the ambulatory patient, it became necessary to construct the present bedside model.

*Construction*—The bedside ergograph as shown in Figure 1, consists of three essential parts:

1 *The framework* consists of a board A, 10" x 56", supported at the proximal end by the bed and the distal end by a support SP reaching to the floor. The Thomas splint S is fixed to this armboard. In this way, a stable cradle is made within which the entire upper extremity below the shoulder rests while the test is being conducted. The splint also serves to immobilize the shoulder.

2 *The weight-lifting system*, consisting of 3- and 5-Kg weights suspended on a cable, which rides over pulleys  $P_1$  and  $P_2$ , at the distal end of the apparatus, then running horizontally over the armboard to join the handle H, which is grasped in the hand of the subject.

3 *The recording system* consists of a stylus ST attached by a string ST<sub>1</sub> through bar B to the weight attachment. As the weight is lifted or lowered, the stylus is lowered or lifted. This is recorded on a moving drum D. The rate of pulling is paced by a metronome set at 2- or 3-second intervals, but constant for each subject.

*Technic for Performing Tests*—The apparatus is fitted to the recumbent subject in such a way that the arm of the patient is slipped into the splint and the shoulder rests on the proximal part of the armboard. The long axis of the apparatus makes an angle of about 30° with the long axis of the bed. The arm and forearm are placed in the anatomic position, *i e*, in full radial

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\* This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and New York University. Read in abstract form before the Committee on Convalescence and Rehabilitation of the Committee on Medical Research, November 15, 1943.

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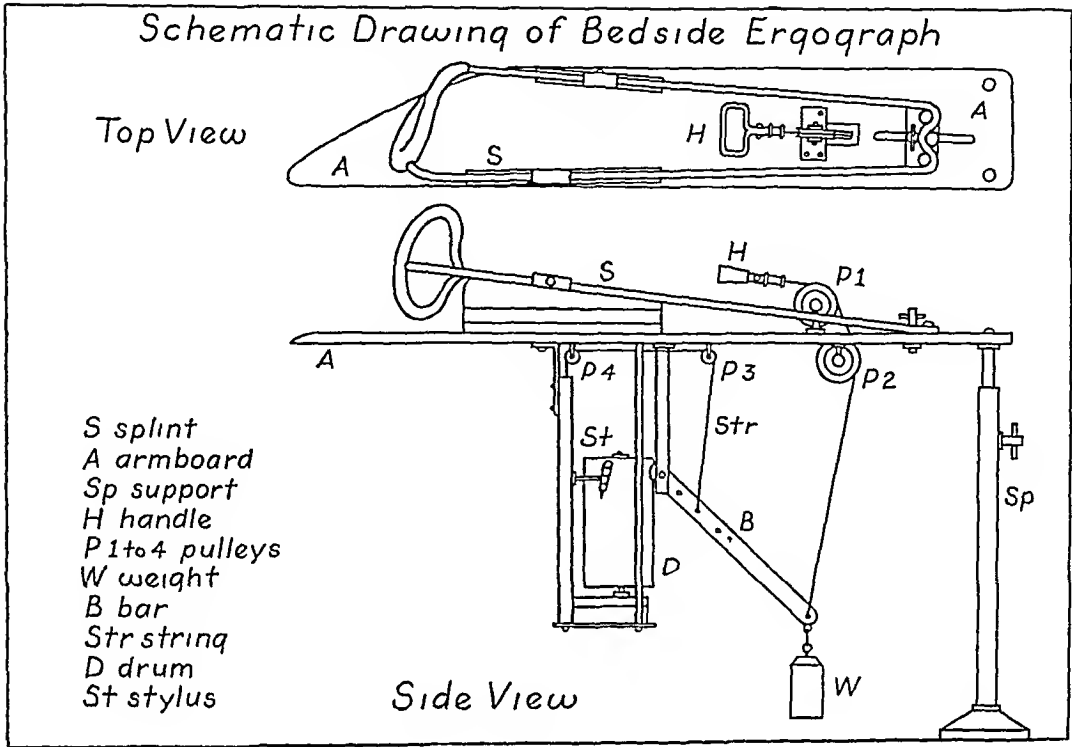


FIG 1—A line drawing of the apparatus

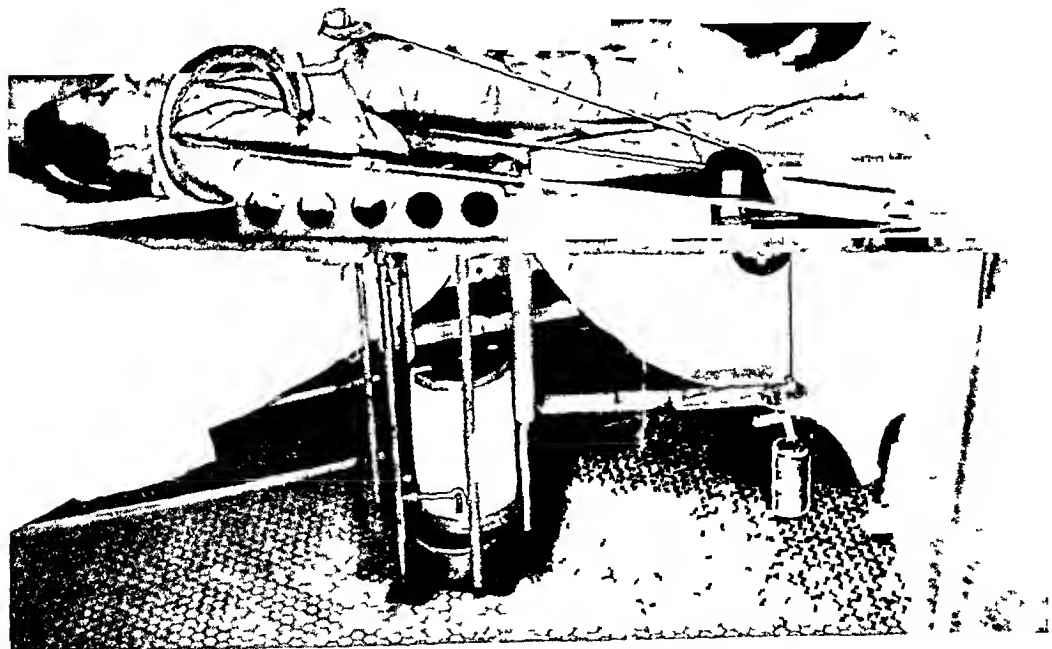
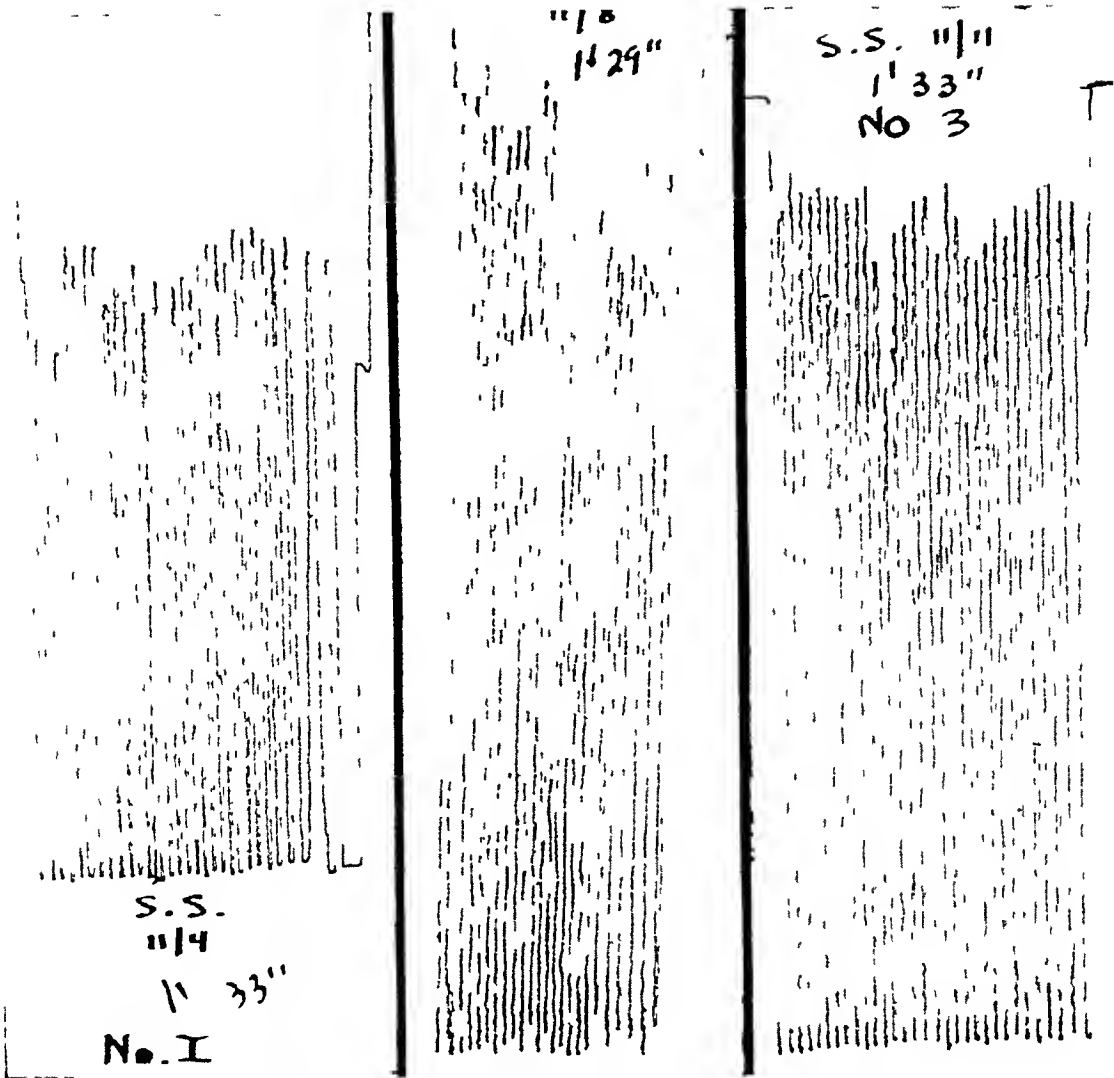
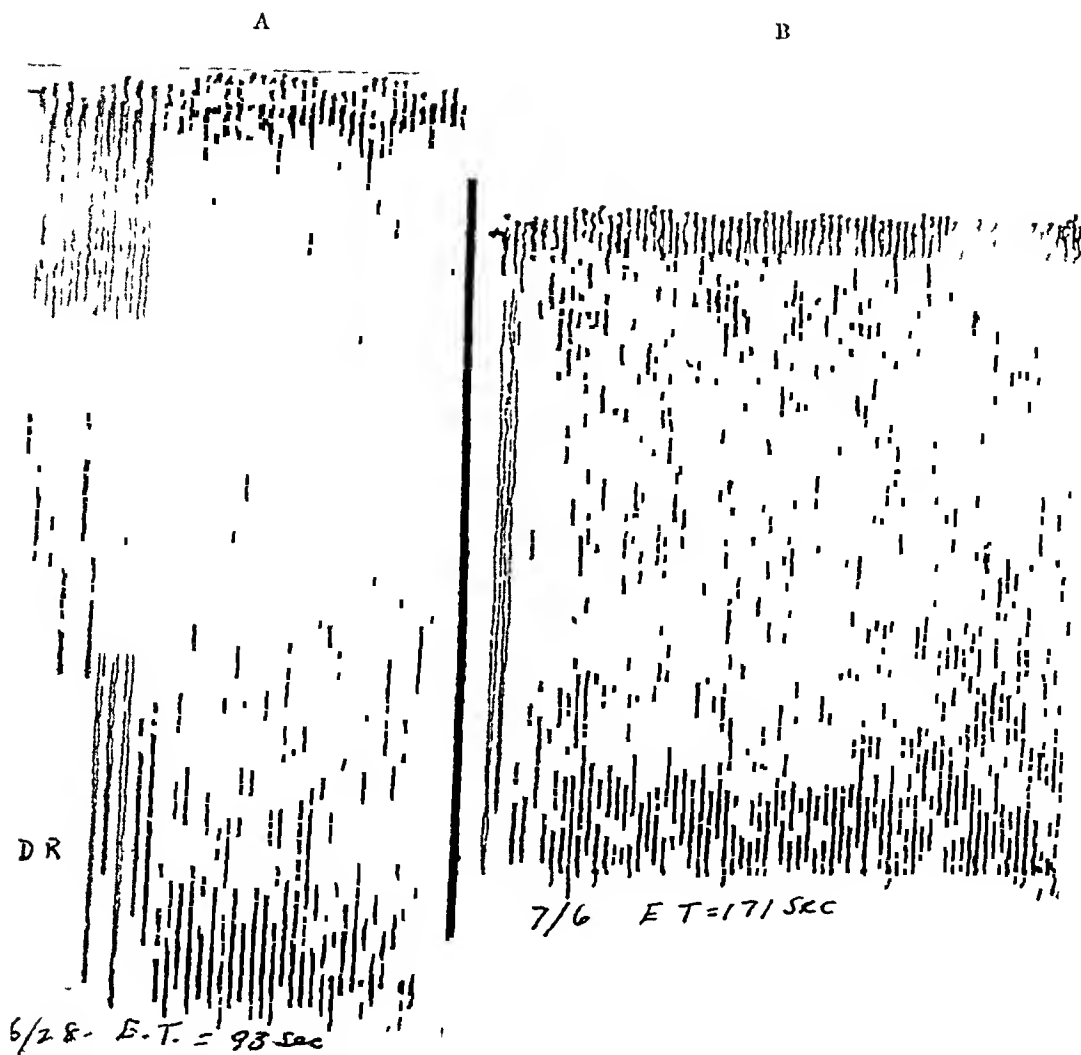


FIG 2—Patient with ergograph fitted

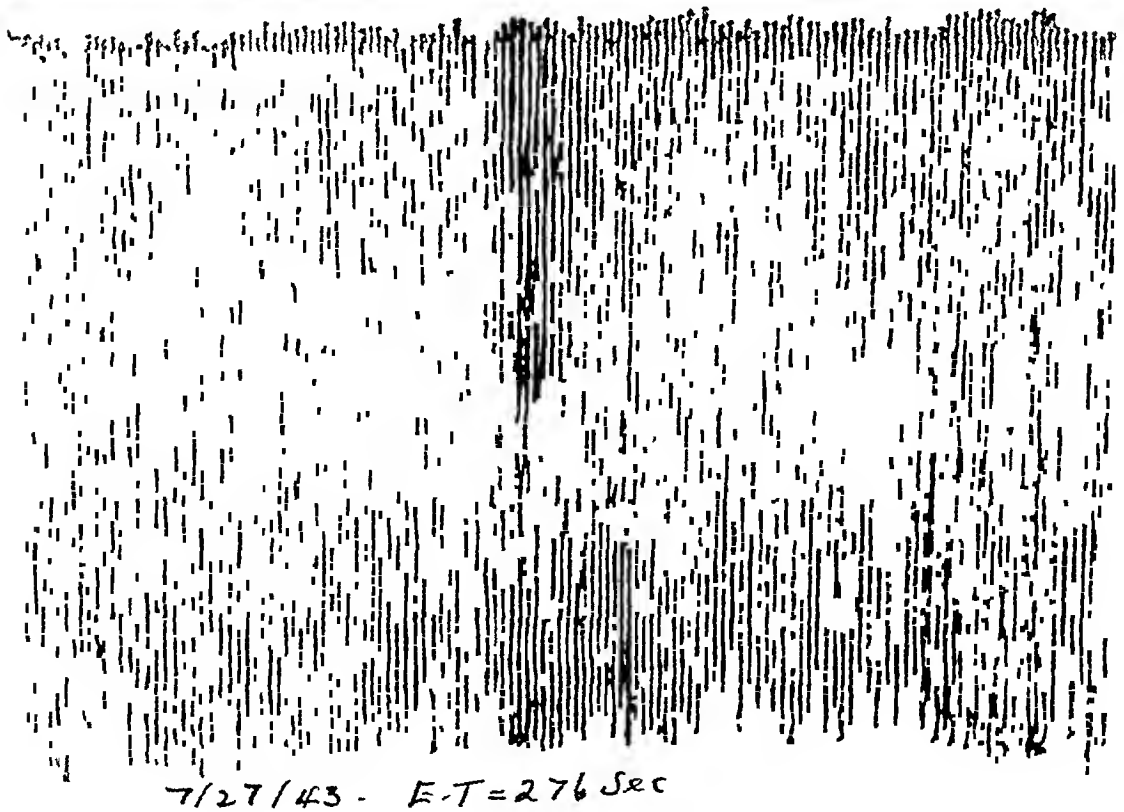
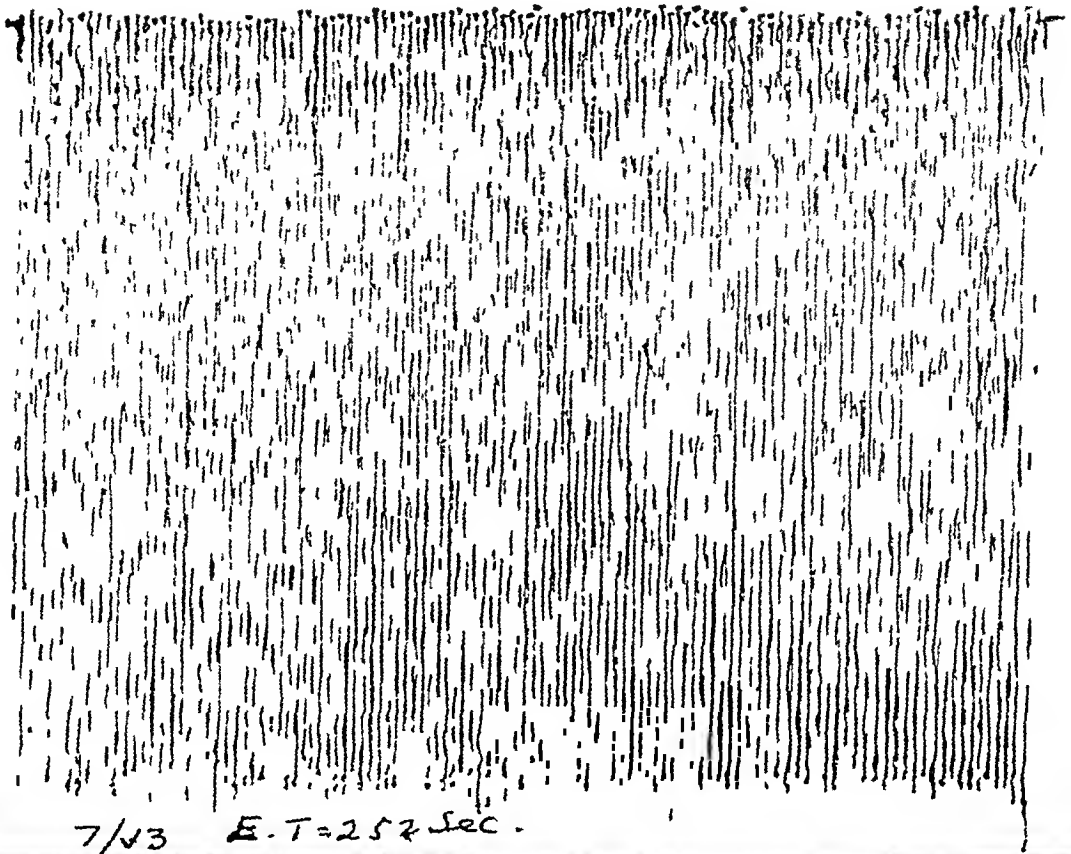


GRAPH 1—Three ergograms of a normal subject taken three and four days apart, showing no significant change in the endurance in the three tests. The ergograph times are, respectively, 93, 90 and 93 seconds.



GRAPH 2—Four ergograms of a patient admitted with malnutrition following a poorly functioning gastrectomy. The initial E.T., Panel I, is 93 seconds, the E.T.'s of Panels II, III, and IV, taken a week apart, after the institution of high caloric and high amino acid feeding and an improvement in nutrition, were, respectively, 171, 252, and 276 seconds. It is to be noted that the amplitude of the excursions is not important since it varies with the length of the lever arm (bar) to which string is attached.

C



D

deviation, the arm is now kept in a fixed position by a linen hammock suspended between the bars of the splint. The handle H is then grasped and the test is ready to start. Fig. 2 is the photograph of a patient with the ergograph fitted. The subject is instructed to pull on the weights up to 90° flexion each time the metronome ticks. The patient stops when he feels a painful fatigue in his biceps muscle. This end-point cannot, therefore, be called entirely objective. The endurance may be expressed either as the number of excursions recorded on the drum, or the length of time from the beginning of the first excursion to the end of the last. This latter, expressed in seconds, is called the ergograph time (E T). Graphs 1 and 2 are respectively the ergograms of a normal person and a patient convalescing from malnutrition.

### SUMMARY

A bedside ergograph has been described to determine the endurance curve of patients postoperatively. While a gross study, it, nevertheless, seems to give significant and consistent results.

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### ANNALS OF SURGERY

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## CONTINUOUS SPINAL ANESTHESIA

## OBSERVATIONS ON 2000 CASES

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EARLY IN 1939, we conceived the idea of continuous spinal anesthesia. A method was formulated, and used on experimental animals. It worked. A great many anesthetics were given dogs, rabbits and monkeys by the method of leaving a needle in the subarachnoid space and giving repeated small doses of procaine hydrochloride. We found that profound anesthesia could be produced and maintained for an unlimited time by this method, without causing any detectable damage to the animal or its functions. Monkeys were kept anesthetized for periods as long as 12 and one-half hours, without any toxic symptoms. It was also observed that large single doses would cause toxic symptoms, and death, but that the same total dosage given over a relatively long period of time caused no toxic symptoms. On April 10, 1939 we administered the first continuous spinal anesthesia to a human being. Since then, we have given well over 2,000 anesthetics by this method, and in this communication we are reporting some of our observations and impressions on these cases.

The method consists merely of making and maintaining a spinal puncture with an initial injection of an anesthetic agent into the subarachnoid space and the subsequent additional injections of the agent as it is needed, much the same as ether is administered, in dosage sufficient to obtain the desired result.

In this series of cases we have used procaine hydrochloride as the anesthetic agent, with one exception, when we used metycaine, because the patient was sensitive to procaine. Procaine was chosen deliberately, because we believe that it is the least toxic of all the drugs used for this purpose and it has the most fleeting action of all the drugs of this nature. By its use, we have been able to have all the advantages of spinal anesthesia, but have been able to use it with a great degree of control and safety.

The disadvantages of the single-dose method of spinal anesthesia are (1) failure of the single dose to produce the level and degree of anesthesia desired, (2) failure of the anesthesia to last for the length of time required to perform the procedure, and (3) the impossibility of removing any of the



agent once it has been injected, should toxic symptoms appear. Continuous spinal anesthesia overcomes the first two disadvantages with ease, and it was accidentally discovered that after the injection had been made, spinal fluid containing the drug could be aspirated and the nerves would promptly recover from the effect of the drug. This has been repeated a number of times, and has been definitely established.

We believe the toxic effects of a spinal anesthetic agent are due to the absorption of the drug into the venous circulation. This can be minimized by the injection of relatively small doses of the drug. Anesthesia is maintained by the concentration of the drug in the spinal fluid which bathes the spinal cord and nerve roots. This concentration may be maintained by relatively small additional doses, given at certain time intervals. In this way, very large doses may be administered with little toxic reaction.

#### TECHNIC OF ADMINISTRATION

The technic of administering continuous spinal anesthesia is very simple. A few pieces of specialized equipment are necessary, which are, (1) a special mattress, five inches thick, with an opening to permit the needle to project from the back of the patient, (2) a special malleable needle, and (3) a 30-inch piece of small bore, thick-walled rubber tubing, with special Luer-Lok connections and stopcock. The other items of equipment used are entirely standard and are usually available in any hospital. Plate I illustrates the fully prepared tray as we use it for continuous spinal anesthesia.

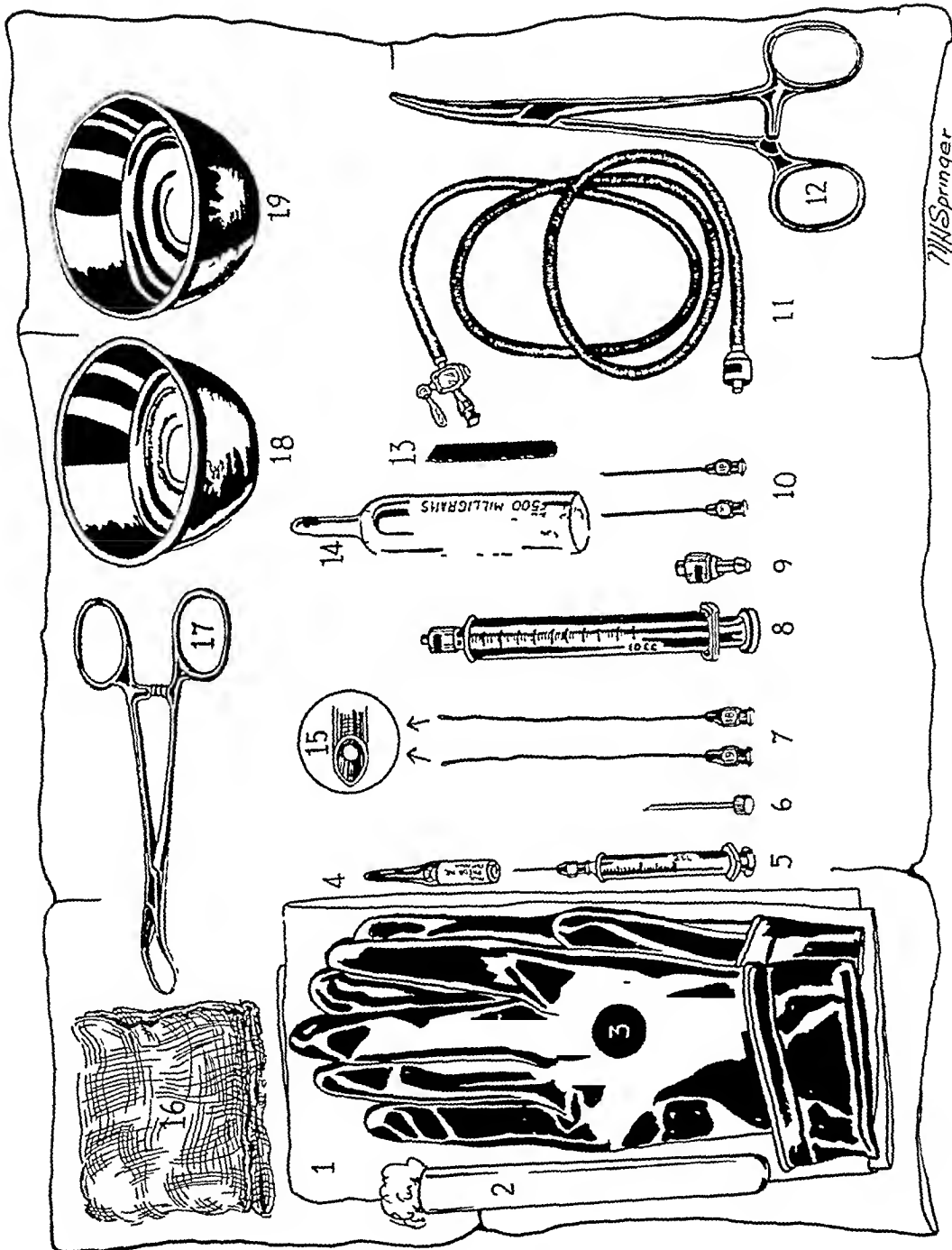
For the puncture, the patient is placed in the lateral decubitus, with the back toward the side of the mattress with the opening. A sterile towel is placed over the upper flank and hip, and the back is prepared with a skin antiseptic. The site of the puncture is selected, chiefly by the individual characteristics of the immediate patient but usually the third or fourth lumbar interspace is chosen. The space that appears to be the easiest through which to make the puncture is the deciding factor. The skin is anesthetized by the introduction of 1 cc of 1 per cent procaine hydrochloride with 50 mg of ephedrine sulphate. The latter drug is used to combat the physiologic lowering of blood pressure which nearly always accompanies the production of spinal anesthesia. The skin is then punctured with a Sise needle introducer. It is important that only the skin be punctured and not the interspinous ligament, for it is the firm grip of the ligament on the needle that maintains the needle in position during the anesthesia. The puncture is now made, and the success or failure of this step determines the success or failure of the method. The needle is a special one, made of a very malleable metal, and therefore, bends with ease. The needle is grasped between the thumb and forefinger, about one-half inch from the point and is started on its way. The position of the needle should be such that it is perpendicular to the back. The only deviation from this simple rule is that the needle may be inclined slightly upwards. The puncture should be made in the exact midline of the body,

and midway between the two lumbar spines. Once the needle has entered the interspinous ligament, it is impossible to change its course, thus, the importance of starting right. The needle is then advanced, always keeping a very short grasp from the skin in order to keep the needle from bending. When the dura is penetrated, the characteristic snap is felt and the puncture is either made or may be completed by advancing the needle a very short distance further. Rotating the needle will often assist in obtaining a free flow of spinal fluid. If a successful puncture is not made, the needle should be withdrawn and a new puncture made. Since we do not use stylets it is important that the patency of the needle be proven before every attempt by flushing it with sterile water or by forcing air through the needle by use of a syringe.

After the puncture has been made, a 10 cc Luer-Lok syringe is attached to the needle and 10 cc of spinal fluid is aspirated. This must be accomplished without too much pulling on the plunger of the syringe. Often the fluid will flow into the syringe, but cannot be aspirated. Gentle traction on the plunger of the syringe is the rule. The syringe is removed, and the needle plug is placed in the needle to prevent the excessive loss of spinal fluid. The 10 cc of spinal fluid is now used to dissolve 500 mg of procaine hydrochloride, which is done in the ampoule by the use of an ordinary intravenous needle and the syringe. After the crystals have dissolved, the solution is drawn up into the syringe and the rubber tubing is attached to the syringe, 2 cc are forced into the tubing, which displaces the air, and fills the tubing with the procaine solution in spinal fluid. Now, the tubing is attached to the spinal needle and the initial injection is made. This dose varies, as will be discussed later, but usually is 3 cc or 150 mg of procaine. After the injection is made, the fluid is aspirated to determine if a satisfactory return flow is present. The stopcock is then closed and the patient is turned on his back, or placed in position for operation. This must be done with care, to prevent the needle from being displaced. The needle should not touch the mattress at any point, nor should it touch the top of the operating table.

The most important factor in the success of continuous spinal anesthesia is the making and maintaining of a good puncture, which is evidenced by the ability to aspirate spinal fluid at any time. If a free return flow is not obtained, the needle may be adjusted through the opening in the mattress and no operation should be started until the puncture is satisfactory.

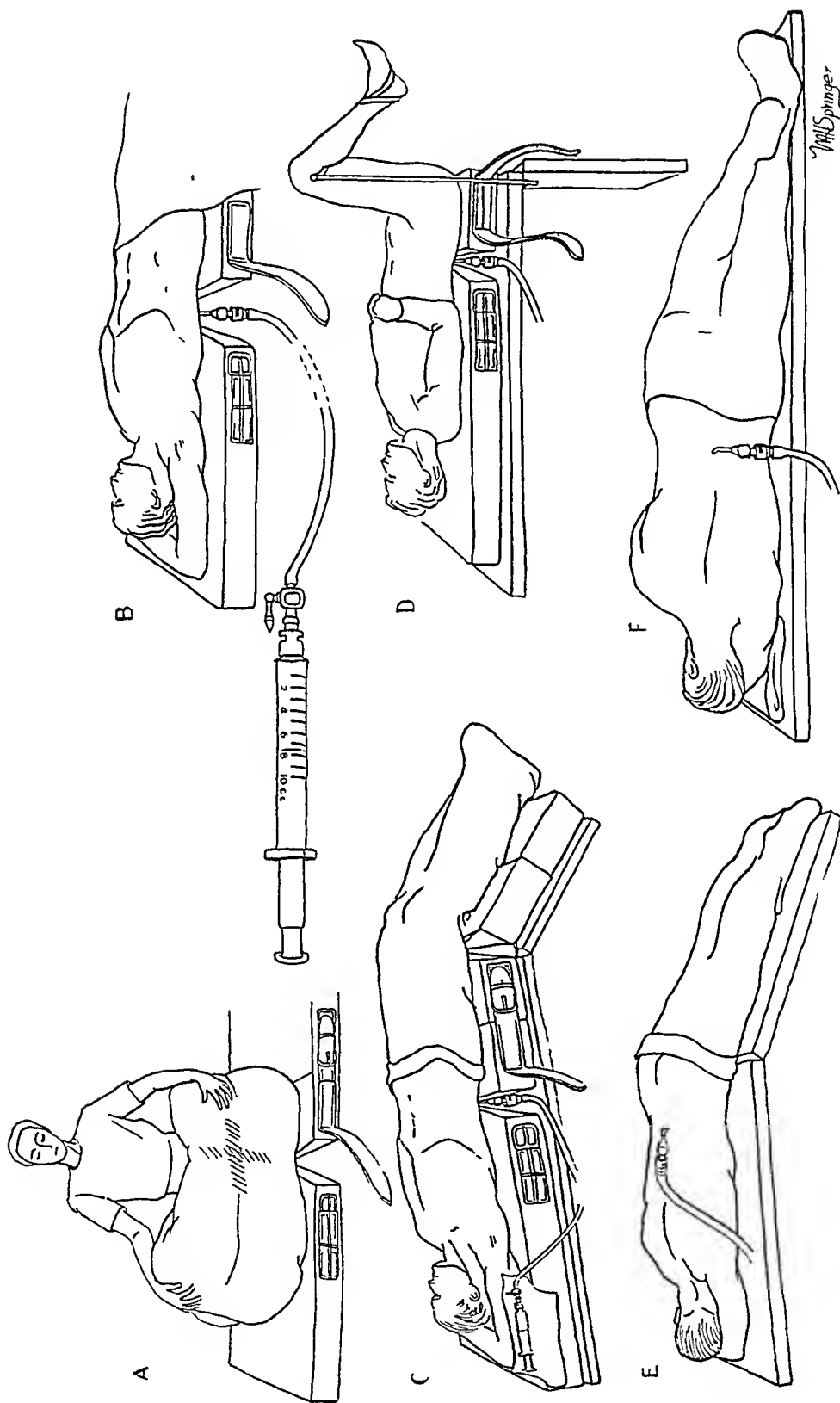
Usually, the effect of the drug is obtained in about 90 seconds after the injection. If after the lapse of two or three minutes, the anesthesia is not satisfactory, the stopcock is opened and another dose is given, which is usually 1 cc, or 50 mg, of procaine. Once satisfactory anesthesia has been produced, it may be maintained by the subsequent injections of 50 mg every 30 minutes. This is not a hard and fast rule, but it will suffice for most cases. The dose is enough, and if more is needed it must be given. We have encountered cases which required additional doses every 15 minutes and needed large doses but many cases do not need it so often nor so much.



W. Springer

PLATE 1 Complete tray for continuous spinal anesthesia

- 1 Two towels, 2 1% povidone iodine solution, 3 Rubber glove, 4 Ampoule containing 1 cc 1% procaine, 5 5 cc ampoule containing 1% procaine, 6 10 cc ampoule containing 1% procaine, 7 10 cc ampoule containing 1% procaine, 8 10 cc ampoule containing 1% procaine, 9 10 cc ampoule containing 1% procaine, 10 10 cc ampoule containing 1% procaine, 11 10 cc ampoule containing 1% procaine, 12 10 cc ampoule containing 1% procaine, 13 10 cc ampoule containing 1% procaine, 14 10 cc ampoule containing 1% procaine, 15 10 cc ampoule containing 1% procaine, 16 10 cc ampoule containing 1% procaine, 17 10 cc ampoule containing 1% procaine, 18 10 cc ampoule containing 1% procaine, 19 10 cc ampoule containing 1% procaine.



## PRELIMINARY MEDICATION

We feel that one of the most important steps in the production of a satisfactory spinal anesthesia is the administration of the proper preliminary medication. Many patients are apprehensive, and fear being awake for the operation. Also the operation of spinal puncture is not without pain in the unsedated patient. Our routine is to give the patient 3 gr of nembutal the night before operation followed by another similar dose three hours before operation. One hour before operation, a hypodermic injection of morphine sulphate gr  $\frac{1}{4}$  and scopolamine hydrobromide gr  $\frac{1}{100}$  is given. This dosage is for the average good-risk adult who is not seriously ill. The dosage is altered to suit the individual case, in the aged and very ill, the dosage is cut sharply. If a patient appears in the operating room with evidence of insufficient sedation, additional doses of morphine are given until the desired effect is obtained. We often give this intravenously. If during the operation, we feel that the patient needs more sedation, it is repeated, usually in  $\frac{1}{8}$  gr doses. It is a well known fact that certain unpleasant sensations are not abolished by spinal anesthesia which are satisfactorily cared for by the use of sedatives. The complaint of the patient of pain in the chest from traction on the cecum during appendicectomy is an illustration of pain which is carried by way of the sympathetics which often involve thoracic segments and could be controlled only by very high spinal anesthesia, but is easily abolished by the judicious use of sedatives.

We have found that children tolerate morphine very well. We have given relatively large doses to children, in divided doses, of course, with no ill effects. We have not encountered respiratory depression from its use. In fact, in this series of cases, we had no complications of a respiratory nature in any of our patients under the age of 15 years of which we had 66.

## TREATMENT DURING THE OPERATION

Other than the preliminary dose of ephedrine given with the procaine for skin anesthesia, we seldom use any vaso-pressor drugs during the course of the anesthesia and operation. It is our firm belief that if a patient is able to stand the surgery, the use of continuous spinal anesthesia will not contribute any deleterious effects. Of course, we have patients whose blood pressure falls quite low during the course of a difficult and shocking operation but it is treated with the thought of treating the operative shock rather than as treating low blood pressure due to spinal anesthesia. For this reason, we gave our patients intravenous glucose solution, blood or plasma to combat this condition and rarely use the vaso-pressor drugs. We anticipate such complications, and never is an operation undertaken on a serious risk, nor is a shocking operation begun until there is flowing into the patient's veins ample fluids, with whole blood plasma, or both immediately available. In this manner we have been able to keep our patients in good condition during the operation. We believe in, and practice, the administration of oxygen throughout the anesthesia and operation.

### ANALYSIS OF CASES

We are presenting 2000 cases in which we have employed continuous spinal anesthesia. Our records show that in three cases we did not get satisfactory anesthesia. One case developed uncontrollable cough during the course of a pulmonary lobectomy. The patient was given cyclopropane during the stage of tugging on the bronchus which caused the coughing. Sensory anesthesia at this time was at the level of the hyoid bone. In the two other cases, faulty technique and a busy schedule are to blame. They were both simple pelvic operations and neither patient was anesthetized to the degree that operation could be undertaken. They were both given ether anesthesia. Let us explain that many of the anesthetics in this series were given by internes and relatively inexperienced anesthetists. Many of the cases in this series have been saved from being failures by the authors making new punctures after what had been thought to be a satisfactory puncture had failed to produce satisfactory anesthesia. In several cases, the patient has been repunctured after the abdomen had been opened and perfectly satisfactory anesthesia obtained.

*Age*—The average age for this group was 35.9 years. The youngest was two days old, who was operated upon for congenital occlusion of the jejunum. A cholecystectomy and choledochostomy for stones on a man, age 87, represents the eldest of the series. With our increased experience with this type of anesthesia in children we have found that it is very satisfactory. In the last 1000 cases, we have had 33 who were ten years or less, and 33 between ten years and fifteen. There were eight cases of five years or less. This has been made possible by the liberal use of morphine in multiple small doses, which we have found is very well tolerated by children. We have not encountered the profound respiratory depression in its use, and we do not fear to use the drug in very young children.

*Length of Operations*—The average length of the operations in this series was 50.1 minutes. The longest procedure was a subtotal pancreatectomy which required five hours and 25 minutes. The shortest procedure was about two minutes for the incision and drainage of an abscess.

*Dosage*—The dosage of procaine for continuous spinal anesthesia is a variable factor. For the operations in this series, the total dosage per case averaged 210.9 mg. The average number of injections was 2.37. The smallest dose was 20 mg. for the amputation of a toe. The largest dose given to one patient was 2200 mg. This was for a hysterectomy which required 35 minutes operating time.

In general for the average case we give an initial dose of 150 mg., which will usually give satisfactory anesthesia for any type of abdominal surgery. This is usually followed by an additional injection of 50 mg. every half hour for the remainder of the operation. However, we encounter many cases which do not require as much, and also many cases which require much larger doses. Children tolerate the drug very well and will require rela-

tively much larger doses than adults. We have on many occasions had to give as much as 250 mg to a child of seven years in order to obtain satisfactory anesthesia to perform an appendectomy, which of course, required no additional doses after anesthesia was produced. We have performed a suprapubic prostatectomy on a man of 85 years, which required 60 minutes with a total dose of 50 mg. The aged and very ill require very small doses. The dosage for any one case may be simply stated as being enough to complete the operative procedure. The condition of the patient is checked frequently, and sufficient dosage is given to produce the desired result. The longest procedure in our series was a subtotal pancreatectomy which required five hours and 25 minutes. This patient received 1450 mg of procaine given in 18 injections.

Our routine procedure calls for the use of a 5 per cent solution of procaine in spinal fluid. Additional doses may be prepared in sterile distilled water or normal saline solution. We have used various dilutions from 1 to 10 per cent, but have found that the 5 per cent solution is the most satisfactory.

#### EFFECT ON BLOOD PRESSURE

The blood pressure, pulse and respiration are checked and recorded every five minutes during the anesthesia. Following the injection of ephedrine along with the procaine which is used to anesthetize the skin for the puncture and to support the blood pressure, we regularly noted an increase in the pressure, which was soon followed by a lowering of the pressure to the original level or slightly below. Unless the operation was of a shocking nature we did not encounter any great fall in the systolic pressure. The average systolic pressure at the beginning of operation for this series was 127 millimeters of mercury. The average systolic pressure at the conclusion of the operation was 114.3 millimeters of mercury. The average fall of systolic pressure was only 12.7 millimeters of mercury. We have had a number of cases in which the blood pressure reached, and maintained, a higher level than that before the anesthesia was begun. This however is an exception to the rule. During the course of operations we have had pressures as low as 40 Mm. Such cases were treated by infusions of glucose solution, blood or plasma. Seldom do we use the vaso-pressor drugs. To cite an example, during the course of a radical mastectomy the blood pressure dropped to 40 Mm. of mercury. The patient's exposed chest wall was covered with hot sponges, no further dissection was done, an intravenous of plasma was started, and in about ten minutes the blood pressure was at 100 Mm. of mercury. The operation was then resumed and completed with the patient in good condition. We feel that instances such as this prove that it is the surgery and not the anesthesia which causes the excessive falls in blood pressure.

*Headache*—The incidence of headache following the use of continuous spinal anesthesia is about the same as following the use of the single-dose

spinal It is a very difficult thing to understand or explain It appears to be more frequent following simple procedures than the more serious ones Our incidence of headache for the entire series is 3.1 per cent This problem is a relatively minor one, which usually responds to simple treatment, such as the administration of aspirin, and we feel that it is a very low price to pay for the advantages of spinal anesthesia, both to the patient and the surgeon

*Urinary Retention*—We have made it a rule to use an indwelling catheter in patients who are submitted to operations which may last a relatively long time and who are receiving intravenous during the operation The bladder often distends during the operation, and if not taken care of tends to encourage retention We also use an indwelling catheter in all vaginal plastic cases Our incidence of retention, excluding the above mentioned cases, is 3.3 per cent for the series

*Pulmonary Complications*—In this series, there were 45 cases which developed pulmonary complications, 27 of these were bronchopneumonia, 11 were lobar pneumonia five were atelectasis, and two were pulmonary embolism

*Nerve System Complications*—One case developed anesthesia of the upper lip immediately following a cystoscopic examination This persisted for two days, then disappeared completely There was nothing unusual about the anesthesia, the level was not high, and we cannot explain this occurrence on any other basis except hysteria There were no other incidences of any type of neurologic complications

*Mortality*—There were 82 deaths in this series of 2000 cases making a gross mortality of 4.1 per cent The average time that elapsed between operation and death was 5.9 days None of these were anesthetic deaths, and we do not feel that the anesthesia was a contributing factor in any of them Thirty-six of those that died were suffering with malignant growths There were 18 deaths from diffuse peritonitis The other deaths were due to many conditions including pulmonary, cardiac, renal and hepatic conditions One death was due to hemorrhage from a far-advanced carcinoma of the cervix the anesthesia being given for the operation of packing of the vagina and rectum We have not had a single death due directly to the use of continuous spinal anesthesia

Table I is an outline of the operations performed on the cases in this series

#### SUMMARY

- 1 We have discussed the experimental work which paved the way to the use of continuous spinal anesthesia

- 2 We have given a detailed account of the technic of continuous spinal anesthesia

- 3 Two thousand operations are reported which have been done under continuous spinal anesthesia, and some of the important observations made on this series are presented



TABLE I

OUTLINE OF 2000 CASES DONE UNDER CONTINUOUS SPINAL ANESTHESIA

Gastro intestinal Operations	
Stomach	68
Appendix	497
Intestinal and colon	97
Biliary tract operations	187
Hernia operations	223
Nerve system operations	34
Gynecologic Operations	
Perineal	93
Abdominopcrineal	206
Abdominal	123
Obstetric operations	140
Urologic operations	89
Proctologic operations	87
Cardiovascular operations	21
Thoracic operations	48
Orthopedic operations	69
Miscellaneous operations	18

CLASSIFICATION

Gastro-intestinal Operations	68
Stomach Operations	
Total gastrectomy	4
Total gastrectomy with splenectomy	1
Subtotal gastrectomy	9
Subtotal gastrectomy and appendicectomy	19
Subtotal gastrectomy and resection of third part duodenum and trans colon	1
Anterior gastro enterostomy	7
Posterior gastro enterostomy	2
Closure duodenal ulcer cholecystectomy and appendicectomy	2
Closure spontaneous rupture of stomach	1
Resection of bleeding gastric ulcer	1
Cholecystogastrostomy	2
Cholecystojejunostomy	1
Biopsy carcinoma of stomach	1
Biopsy head of pancreas	1
Subtotal gastrectomy and cholecystectomy	5
Closure perforated ulcer	7
Closure perforated gastric carcinoma	1
Gastrostomy	1
Subtotal pancreatectomy	1
Resection tail of pancreas and splenectomy	1
Appendix Operations	497
Appendicectomy	395
Appendiceal abscess drainage	15
Appendicectomy and excision of ovarian cyst	33
Appendicectomy and salpingo oophorectomy	11
Appendicectomy and uterine suspension	18
Appendicectomy and lysis adhesions	20
Appendicectomy and reduction of torsion of omentum	1
Appendicectomy and excision of varicoccle	1
Appendicectomy and myomectomy	1
Appendicectomy and cecostomy	1
Appendicectomy and fecal fistulectomy and incisional herniorrhaphy	1
Intestinal and Colon Operations	97
Abdominal and perineal resection of rectum	12
Closure of colostomy	6
Mikulicz resection splenic flexure	3
Mikulicz resection of sigmoid	8
Resection ileum—intestinal obstruction	5
Lysis of adhesions and reperitonealization for intestinal obstruction	27
Incision and drainage subhepatic abscess	1
Abdominal section—biopsy of liver	10
Resection sigmoid primary anastomosis	1
First stage Lahey	3

TABLE I (Continued)

Second stage Laley	1	
Colostomy	6	
Cecostomy	2	
Closure of cecostomy	1	
Resection ileum for intussusception	1	
Ileotransverse colostomy	5	
Ileosigmoidostomy	1	
Closure of fecal fistula	1	
Excision of duodenal diverticulum and appendicectomy	1	
Excision of Meckel's diverticulum	1	
Exteriorization of sigmoid for diverticulitis	1	
Biliary Tract Operations		187
Cholecystectomy	49	
Cholecystectomy and lysis of adhesions	25	
Cholecystectomy and appendicectomy	57	
Cholecystectomy and T-tube drainage of common bile duct	35	
Cholecystectomy and hysterectomy	2	
Cholecystectomy and oophorectomy	2	
Cholecystectomy and choledochojejunostomy and jejunojejunostomy	2	
Cholecystostomy	2	
Choledochostomy	6	
Cholecystogastrostomy and biopsy of head of pancreas	2	
Cholecystojejunostomy	1	
Cholecystectomy and anterior gastro-enterostomy	1	
Excision of stricture of common bile duct	1	
Excision of tumor of common bile duct	1	
Repair of divided common bile duct	1	
Hernia Operations		223
Unilateral inguinal herniorrhaphy	101	
Right inguinal herniorrhaphy and appendicectomy	19	
Strangulated inguinal hernia	6	
Bilateral inguinal hernia	23	
Femoral herniorrhaphy	9	
Ventral herniorrhaphy	5	
Incisional herniorrhaphy	11	
Inguinal herniorrhaphy and excision of hydrocele	1	
Umbilical herniorrhaphy	4	
Umbilical herniorrhaphy and appendicectomy	3	
Incisional herniorrhaphy cholecystectomy and appendicectomy	1	
Incisional herniorrhaphy and hysterectomy	1	
Incisional herniorrhaphy and myomectomy	1	
Femoral herniorrhaphy and closure of ileostomy	1	
Inguinal herniorrhaphy and D and C cauterization of cervix and appendicectomy	1	
Inguinal herniorrhaphy and orchidectomy	1	
Herniotomy and appendicectomy	1	
Herniotomy and exteriorization of gangrenous ileum	1	
Richter's hernia	1	
Nerve System Operations		34
Presacral neurectomy	1	
Presacral neurectomy and appendicectomy	1	
Presacral neurectomy uterine suspension and appendicectomy	17	
Presacral neurectomy and D and C	2	
Presacral neurectomy and hysterectomy	3	
Bilateral lumbar ganglionectomy	3	
Cervical ganglionectomy	2	
Thoracic ganglionectomy	1	
Unilateral thoracic and lumbar ganglionectomy	3	
Exploration and freeing of adhesions of common peroneal nerve	1	
Gynecologic Operations		93
Perineal		
Dilatation and curettage	29	
Dilatation and curettage radium	20	
Induction of therapeutic abortion	1	
Dilatation and curettage and biopsy	2	
Dilatation and evacuation	2	
Vaginal hysterectomy and perineorrhaphy	10	
Fothergill anterior and posterior colporrhaphy and perineorrhaphy	4	

TABLE I (Continued)

Plastic repair	22	
Excision of anterior vaginal wall	1	
Vesicovaginal fistula	1	
Vaginal packing for hemorrhage (carcinoma of cervix)	1	
Abdominal and Perineal		206
Plastic and section	105	
Plastic and appendectomy	14	
Plastic and hysterectomy	7	
Dilatation and curettage cauterization of cervix hysterectomy salpingo oophorectomy and appendectomy	76	
Plastic and section hysterectomy and cholecystectomy	3	
Amputation of cervix and cholecystectomy	1	
Abdominal		123
Supravaginal hysterectomy	22	
Unilateral salpingo oophorectomy	14	
Bilateral salpingo oophorectomy and appendectomy	5	
Unilateral salpingo oophorectomy and appendectomy	4	
Hysterectomy bilateral salpingo oophorectomy and appendectomy	49	
Excision ovarian cyst and appendectomy	10	
Hysterectomy and appendectomy	6	
Uterine suspension and appendectomy	4	
Anastomosis of uterine tube	1	
Biopsy carcinoma of uterus	1	
Bilateral oophorectomy and resection of ileum	1	
Drainage of pelvic abscess	1	
Supravaginal hysterectomy and presacral neurectomy	2	
Resection of ovarian cysts and lysis of adhesions	2	
Myomectomy and appendectomy	1	
Obstetric Operations		140
Cesarian section	73	
Cesarian section and ligation of tubes	55	
Cesarian section and appendectomy	3	
Cesarian section and incisional hernia	2	
Cesarian section and lysis of adhesions	5	
Cesarian section and repair of ruptured uterus	1	
Vaginal cesarian section	1	
Urologic Operations		89
Suprapubic prostatectomy	17	
Perinephritic abscess	1	
Ureterolithectomy	5	
Nephrectomy	7	
Excision of varicocele	6	
Nephrolithectomy	1	
Hydrocele and circumcision	1	
Hydrocele	3	
Orchidectomy	5	
Lysis of adhesions obstructing ureter	1	
Aberrant renal vessels causing obstruction	1	
Bilateral vasotomy	1	
Cystotomy	2	
Excision cyst urachus appendectomy	1	
Excision epididymis	1	
Nephropexy	2	
Meatotomy and plastic of glans penis	1	
Excision of diverticulum bladder	1	
Excision of carcinoma of bladder	1	
Cystectomy	1	
Vesico abdominal fistulectomy	1	
Cystoscopy	22	
Dilatation of ureteral stricture	1	
First stage Torek	4	
Second stage Torek	2	
Proctologic Operations		87
Hemorrhoidectomy	62	
Excision of fistula in ano	13	
Incision and drainage ischiorectal abscess	1	
Biopsy and fulguration anorectal tuberculosis	1	

TABLE I (Continued)

Fulguration anorectal tuberculosis	2	
Sigmoidoscopic examination	2	
Sigmoidoscopic and biopsy	1	
Repair of complete laceration rectal sphincter	1	
Orthopedic Operations		69
Sequestrectomy osteomyelitis	1	
Excision head of metatarsal	1	
Bilateral amputation hammer toe	2	
Excision internal semilunar cartilage	5	
Reduction fracture of 5th metatarsal	1	
Excision pilonidal sinus	32	
Excision benign tumor of leg	7	
Excision coccyx	6	
Mid thigh amputation	6	
Open reduction fracture great toe	1	
Excision bunions	1	
Excision exostosis	1	
Excision of lipoma thigh	1	
Excision popliteal bursa	1	
Removal of transverse process 5th lumbar vertebra	1	
Cardiovascular Operations		21
Ligation of patent ductus arteriosus	1	
External iliofemoral arteriovenous aneurysm	1	
Right femoral embolectomy	1	
Bilateral saphenous ligation	11	
Unilateral saphenous ligation	7	
Thoracic Operations		48
Revision of wound	1	
Anterior thoracoplasty 1st stage	6	
Posterior thoracoplasty 1st stage	5	
Posterior thoracoplasty 2nd stage	6	
Posterior thoracoplasty 3rd stage	3	
Posterior thoracoplasty 4th stage	1	
Pulmonary lobectomy	2	
Pneumonectomy	2	
Radical mastectomy	9	
Simple mastectomy	1	
Excision of breast tumor	10	
Breast plastic	2	
Miscellaneous Operations		18
Incision and drainage abdominal abscess	5	
Repair of excoriation	3	
Incision and drainage of abscess	2	
Lipectomy and ventral herniorrhaphy	1	
Excision of carbuncle	1	
Excision of sarcoma of popliteal space	1	
Resection of inguinal lymph nodes	1	
Resection of strangulated omentum	1	
Removal of bullets from leg	1	
Incision and drainage stab wound thigh	1	
Excision of ulcer of abdominal wall	1	

4 The use of continuous spinal anesthesia in children has been indicated

5 We wish to emphasize the adequacy, safety and controllability of this method

6 The fact that the dosage is a most variable factor is emphasized, and we reiterate that the dose is enough to produce the desired level and degree of anesthesia

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# CONTINUOUS SPINAL ANESTHESIA FOR LABOR AND DELIVERY<sup>1</sup>

## A PRELIMINARY REPORT

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IN 1942 HINGSON AND EDWARDS<sup>1</sup> through a familiarity with the continuous spinal anesthesia method introduced by Lemmon,<sup>2</sup> first published their report on continuous caudal analgesia in obstetrics. The effect of this work was to stimulate anew, widespread interest in painless childbirth. Both the advantages and the inherent dangers of the method have been subjected to critical analysis by many investigators. It is generally agreed that the most important cause of failure is the inability to insert the needle properly into the caudal canal. We decided, therefore, to investigate the possibility of continuous spinal anesthesia. While the method has been used for some time in cesarean section, this is the first attempt, to our knowledge, to apply it to labor and vaginal delivery. This preliminary report is based on our experience in its use on fifty cases.

## METHOD

The technic employed has not been entirely uniform. In the first five cases we followed the principle as originally advocated by Lemmon<sup>2</sup> using a standard continuous spinal set with a 19 gauge malleable nickel needle. In our desire to keep the anesthesia as low as possible the third or fourth lumbar interspace was chosen as the site of injection. The anesthetic agent was procaine hydrochloride 5 per cent in normal saline. The standard dose was 15 mg. With this technic relief of pain usually occurred within five minutes. However, in most instances the patient experienced dull pain in the back with each uterine contraction. This unfavorable reaction prompted us to inject at a higher level. When this was done the relief of pain was complete within three minutes. While the choice of the first or second interspace may seem to many unnecessarily high, this location is physiologically correct. The truth of this statement can be verified by examination of the chart in Figure 1 showing the sensory pathways to the uterus. The average interval between injections using a 5 per cent procaine hydro-

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\* We are indebted to Dr. Robert A. Hingson for his cooperation in the preparation of this report.

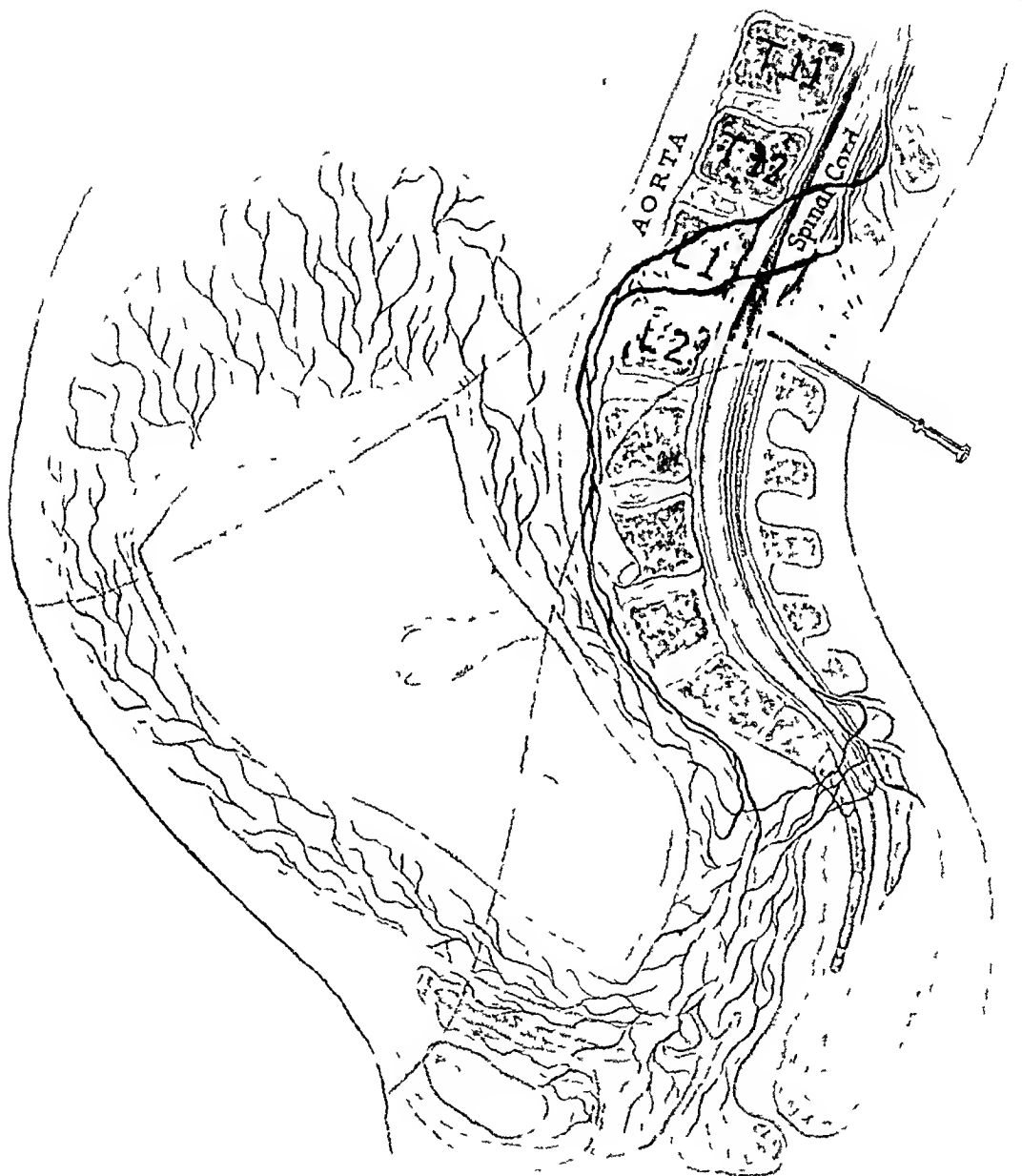


FIG. 1—Sagittal section of a pregnant woman showing spinal needle in place between the first and second lumbar vertebrae. Note the needle's proximity to (1) the eleventh and twelfth thoracic nerves which carry uterine sensory fibers, and (2) the second, third, and fourth sacral nerves which carry sensory fibers from the cervix and lower birth canal.

Puncture of the dura at a higher level might result in injury to the spinal cord. Motor fibers, not shown, are involved if the anesthesia blocks the sixth or higher thoracic nerves.

chloride was 30 to 40 minutes. Two per cent procaine hydrochloride was then tried. This was found to be unsatisfactory for two reasons, namely, a higher dosage requirement (20 mg) and a shorter interval between doses (15 to 20 minutes). Despite the fact that our results in these early cases were encouraging, we were not satisfied with this method primarily because of the length of the needle and the difficulty in keeping it in the subarachnoid space with the inevitable motion of the patient while in labor.

Our present technic is as follows: the patient is placed on either side with the back flexed, which is the most favorable position for lumbar puncture. After a thorough surgical preparation a 2.5- or 3-inch malleable steel needle of the type used by Hingson and Edwards in caudal anesthesia is inserted into the first or second lumbar interspace. A free drip of spinal fluid is obtained. The back is then extended in order to fix the needle firmly. The needle is then connected by rubber tubing to a 20 cc Luer-Lok syringe with cut off valve containing 1.5 per cent Metycaine in Ringer's solution. The standard dose is 15 mg (1 cc) which is repeated at necessary intervals to secure complete relief of pain (25 to 40 minutes). The height of the anesthesia level is tested at frequent intervals. We have found the sensory loss should extend 2 to 3 cm above the umbilicus. Should the level rise above this point, there is danger of causing a cessation of uterine contractions. It is important that while we have found this dosage sufficient to produce anesthesia, complete motor paralysis does not occur. In practically all cases the needle was withdrawn when the patient was placed on the delivery table, due to the fact that a split-mattress was not available. In our opinion this is undesirable because it destroys an important safety factor, namely the ability to withdraw the anesthetic agent in the event of any untoward effect of the anesthetic solution.

In several patients spinal fluid was withdrawn following the delivery in order to determine the Metycaine content. Report of one specimen from the laboratory of Eli Lilly and Company is as follows:

"J. S., age 31, para 1—continuous spinal July 6/44, 8 cc Spinal fluid withdrawn following delivery. The specimen as measured in our laboratory contained 7.5 cc. The concentration was 4.9 mg "metycaine" (*gamma* [2-methylpiperidino]-propyl benzoate hydrochloride Lilly) per cc or a total quantity of about 37 mg. This patient received 60 mg of metycaine over a period of two hours."

The presence of this concentration of the anesthetic in the spinal fluid serves to emphasize the desirability of keeping the needle in place until completion of the delivery.

#### RESULTS

Complete relief of pain was obtained in 40 cases, or 80 per cent, partial relief of pain was obtained in eight cases or 16 per cent. Two cases, or 4 per cent, were complete failures despite the fact that in each instance a free flow of spinal fluid was obtained and an adequate dose of anesthetic administered. In three cases, or 6 per cent the anesthetic was discontinued because of



## SPINAL AND CONTINUOUS SPINAL ANESTHESIA

Metvcaïne, Procaine, Pontocaine Nupercaine, Monocaine

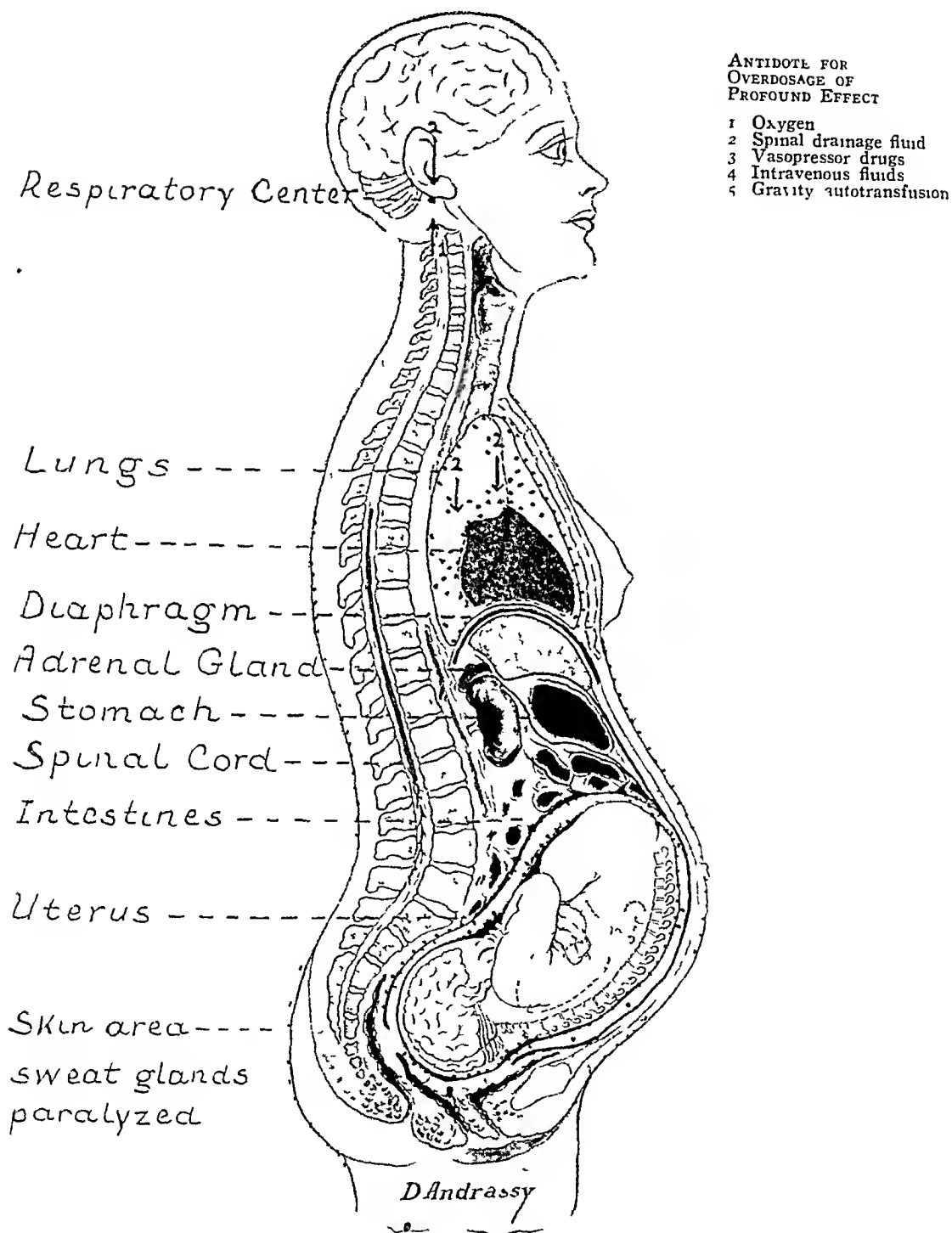


FIG 2—RED indicates stimulation and BLUE indicates depression of maternal and fetal organs. Solid color indicates intensified action, Dotted color indicates moderate action and Outline dots indicate minimal action. Numbers (1 and 2) on ascending and descending arrows indicate sequence of stimulation and depression.

—From "Control of Pain in Childbirth," by Clifford A. Lull, M.D. and Robert A. Hingson, M.D.  
J. B. Lippincott Company, Philadelphia, Pa.

ETHYL ETHER

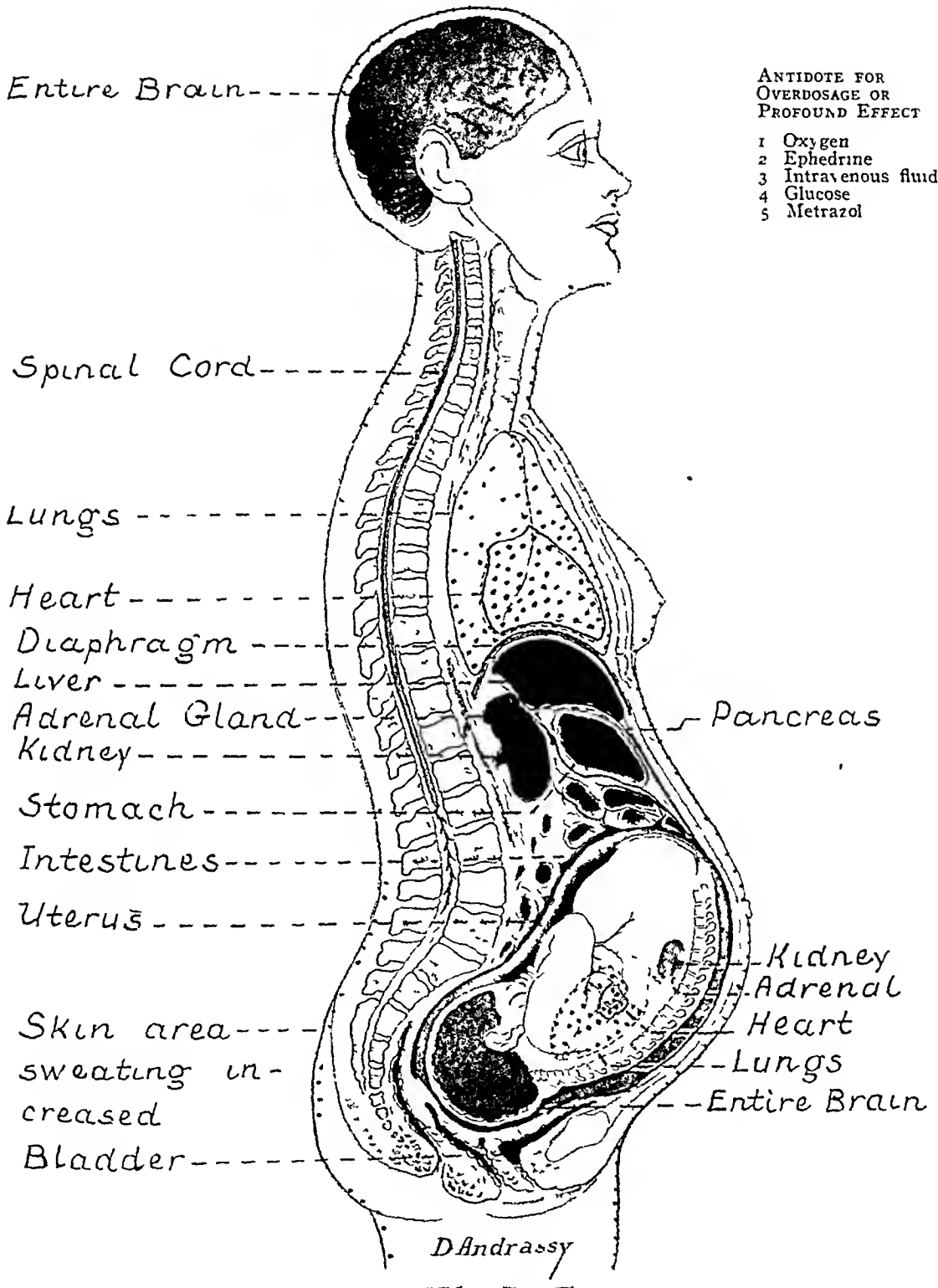


FIG 3—RED indicates stimulation and BLUE indicates depression of maternal and fetal organs. Solid color indicates intensified action, Dotted color indicates moderate action, and Outline dots indicate minimal action. Numbers (1 and 2) on ascending and descending arrows indicate sequence of stimulation and depression.

—From "Control of Pain in Childbirth," by Clifford A. Lull, M.D. and Robert A. Hinason, M.D., J. B. Lippincott Company, Philadelphia, Pa.

dislodgment of the needle from the subarachnoid space Six cases or 12 per cent required inhalation anesthesia for delivery Included in this group are the two complete failures previously mentioned, one patient who experienced pain during the decomposition and extraction of the second of twins, and the three cases in whom the needle was dislodged (in two of these the episiotomy was repaired without supplementary anesthesia)

#### EFFECT ON LABOR

It is impossible to analyze accurately the effect on the duration of labor in a series this small It is our impression that labor is not lengthened if certain prerequisites are observed The patient must be in active labor and have reached a point where she is suffering severe pain, not merely the discomfort of early first-stage labor The presenting part should be engaged and on a level with the ischial spines This applies equally to multipara as well as nullipara The cervix should be effaced and 4 cm dilated before instituting the method in nullipara Dilatation of 2 cm is satisfactory for multiparous patients Failure to observe these rules will invariably result in prolongation or even cessation of labor

In no case did we observe any interference with either the frequency or force of uterine contractions Furthermore, we were impressed by the apparent acceleration of cervical dilatation This would seem to at least suggest that under proper conditions the first stage of labor is shortened by this method While the mechanism of the first stage of labor is not appreciably altered, it must be frankly admitted that the normal mechanism of the second stage is in most instances delayed One patient delivered spontaneously, in the remaining 49 operative delivery was necessary or an incidence of 98 per cent Forty-three cases or 86 per cent were delivered by low forceps, six cases or 12 per cent were delivered by mid-forceps Every instance of mid-forceps application occurred in occiput posterior positions

It is our impression that mid-forceps is the rule in occiput posterior positions in continuous spinal anesthesia because the relaxed pelvic floor permits extension of the head with resultant arrest

In all fairness, it should be stated that despite the high incidence of forceps delivery, these were greatly facilitated by the complete pelvic relaxation which was obtained For example, no sulcus tears were encountered in the mid-forceps group We do not believe this statement can be made in cases delivered under inhalation anesthesia Furthermore, with proper application of forceps and episiotomy, normal pelvic anatomy should be preserved We were unable to note any deviation from the normal third-stage mechanism In all instances the placenta separated completely and promptly (usually within three minutes) and was expressed by the simple procedure of traction and fundal pressure No case of retained placenta occurred

While the blood loss was not measured, we believe that we may state with accuracy that it was less than normal, *i e.*, less than 250 cc In no case did the uterus fail to contract firmly at the end of the third stage, thus

precluding the necessity for the routine use of oxytoxics. We do not advise the administration of either pituitrin or any ergot derivative until termination of the third stage. Failure to observe this precaution may result in retained placenta.

#### EFFECT ON THE MOTHER

Ninety per cent of the mothers reacted favorably to this method and were enthusiastic over the dramatic relief of pain. Approximately 10 per cent, mainly multiparae, were either emotionally or intellectually unsuitable for continuous spinal anesthesia. While their behavior was entirely satisfactory during labor, it was difficult to convince them upon arrival in the delivery room that they would experience no pain during the actual birth of the child. There were no instances of broken needles. Infections, severe circulatory collapse or sensitivity to the various drugs were not encountered. In a few cases primary unilateral anesthesia occurred. This was easily overcome by additional dosage and placing the patient on the opposite side. Little or no alteration of blood pressure occurred in the vast majority of cases. In only three patients did the blood pressure drop to a serious level. Rapid restoration was effected by the administration of oxygen, a vasoconstrictor drug and elevation of the lower extremities to a 90 degree angle. Twelve per cent of the group were hypertensive because of toxemia. In each instance the blood pressure was lowered and the urinary output increased under continuous spinal anesthesia.

One patient developed postpartum eclampsia. She was admitted to the hospital in labor complicated by severe toxemia, her blood pressure being 180/120. During ten hours of spinal anesthesia the blood pressure dropped to 140/100 and the urinary output was 1200 cc. (Spinal was instituted early to observe its effect in severe toxemia.) It is our belief that the single convulsion which followed did not result from the anesthesia.

Twenty-two cases, or 42 per cent, experienced rather severe but transient headache which was relieved by mild analgesics. This complication could be prevented in most instances by having the patient remain in the supine position without a pillow for 48 hours postpartum. There were no instances of backache or pain in the legs during the postpartum period. Twelve cases or 24 per cent had urinary retention following delivery. All of these were transient, disappearing by the end of 72 hours. This incidence is no higher in our experience than with other anesthetics. Maternal morbidity in our series was 6 per cent. There were no maternal deaths.

#### EFFECT ON THE INFANT

Spinal and continuous spinal anesthesia have no adverse effect upon the foetus. The illustrative charts reproduced here show the comparative effect on both mother and child of spinal anesthesia and ethyl ether. The marked contrast between the two graphically demonstrates the superiority of spinal anesthesia. Dr. Kenneth A. Heard of the University of Toronto has stated "He who denies the baby the safety of spinal anesthesia must be prepared

to accept the responsibility for its protection from ether." There were 51 live babies in this series and no stillbirths. Respiration was spontaneous and immediate and all infants cried lustily. Cyanosis did not occur in a single case. One infant died 72 hours postpartum. This occurred in a seven months premature and in our opinion can not be attributed to the anesthesia.

#### INDICATIONS AND CONTRAINDICATIONS

Although our series is small and our experience with this method limited, we feel that continuous fractional spinal anesthesia is especially indicated in the following conditions: (1) prematurity, (2) some cases of heart disease, (3) hypertensive toxemia, (4) pulmonary disease, such as tuberculosis, (5) previous cervical and vaginal laceration because of its relaxing effect on the lower uterine segment, pelvic floor and perineum.

Contraindications may be divided into local, general and obstetric. The local contraindications are: (1) deformity of the spine or disease of the spinal cord, (2) local infections at or near the site of injection. The general contraindications are: (1) marked obesity, (2) history of sensitivity to the drug, (3) those emotionally unsuited, (4) severe anemia.

The obstetrical contraindications are: (1) nonengagement of the presenting part, (2) cephalopelvic disproportion, (3) known fetal deformity or dead baby, (4) placenta previa, (5) internal podalic version.

#### COMMENT

Continuous spinal anesthesia for labor and vaginal delivery is still in the experimental stage. We urge extreme caution in its use. It should only be employed either in the hands or under the direction of one completely familiar with the technique and in a well equipped institution. All precautions to safeguard the patient's welfare should be taken. Oxygen, vasoconstrictor drugs, stimulants and intravenous fluids should be immediately available at all times. Because of the high incidence of operative delivery, continuous spinal anesthesia should not be attempted by the untrained obstetrician. The method is time-consuming and requires constant personal supervision. It is both unfair and dangerous to give the initial injection and then place the responsibility for its continuation in the hands of an intern or nurse. We feel that continuous spinal anesthesia affords the patient the additional safety factor of withdrawal of the anesthetic agent should any untoward effect occur. This is in contrast to caudal or single injection spinal in which this is impossible.

#### SUMMARY

1 Fifty cases of continuous fractional spinal anesthesia for labor and delivery are presented and discussed.

2 Comparison between the various drugs seems to indicate the superiority of 1.5 per cent metycaine in Ringer's solution.

3 It has been shown that the most favorable site of injection is the first or second lumbar interspace.

4 Premature institution of the method invariably results in prolongation or cessation of labor

5. The patient should be in active labor with the presenting part in mid pelvis and the cervix 2 to 4 cm dilated, depending upon the parity

6 The progress of the first stage is apparently accelerated

7 The second stage of labor is altered, and the incidence of operative delivery is greatly increased

8 The third stage of labor proceeds normally, and the blood loss is minimal

9 This anesthesia is without adverse effect on the baby

10 We do not advocate this method as a routine procedure and urge caution in its employment. While no serious complications occurred in this series further trial is necessary to evaluate its future place in obstetrical anesthesia

#### REFERENCES

<sup>1</sup> Hingson, R. A., and Edwards, W. B. Continuous Caudal Anesthesia in Obstetrics. *Am J Surg*, 57, 459, 1942

<sup>2</sup> Lemmon, W. T. A Method for Continuous Spinal Anesthesia. *ANNALS OF SURGERY*, 111, 141, 1940, *idem, ibid* 120, 129, August, 1944

# THE USE OF THIOURACIL IN THE PREPARATION OF PATIENTS WITH HYPERTHYROIDISM FOR THYROIDECTOMY\*

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THE PREPARATION of thyrotoxic patients for thyroidectomy has undergone a gradual evolution based on the use of physical or chemical agents intended to correct the underlying physiologic abnormality and bring the patient to surgery in as nearly normal a state as possible. Bed rest alone, with adequate sedation, accomplished a minimal but significant change in this direction. The introduction of the use of iodine for this purpose by Plummer,<sup>1</sup> in 1923, marked a signal advance, with a resultant lowering of operative morbidity and mortality.

During the "iodine period" of thyroid surgery in the years which intervene from Plummer's contribution until the present, refinements in surgical technique with modification of the one-stage subtotal thyroidectomy have been superimposed on iodine treatment with a view to more adequate preparation for the final removal of the gland. Pole ligation and staged thyroidectomy, employing various techniques and intervals, have found a useful place in occasional cases. However, the fundamental problem remained of a patient undergoing operation suffering from a metabolic abnormality greatly aggravated by the physiologic stress and local manipulation incident to thyroidectomy. Attempts to reduce the importance of these latter factors by variation in anesthetic agents have led to the use of a number of anesthetic and operative techniques which only ameliorate but do not solve the problem.

In 1941 and 1942<sup>2,3</sup> the MacKenzies and McCollum reported that sulfamylguanidine produced goiters and depressed the basal rate of oxygen consumption in experimental animals. Richter and Clisby<sup>4</sup> made similar observations using thiocarbamide. These observations formed the basis for the use of an entirely new series of chemical agents possessing potent but at that time poorly understood action on the thyroid gland.

Astwood<sup>5</sup> studied a number of these goitrogenic agents and determined that

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\* Aided in part by a grant from the Josiah Macy, Jr. Foundation

2-thiouracil was among the most effective and that unlike goitrogens of the thiocyanate group the hyperplastic effect on the gland was not abolished by the coincident administration of iodine. To Astwood, also, belongs the credit for first using agents of this class in the treatment of thyrotoxicosis, his work with thiouracil led to our employment of the drug as a means of preparing thyrotoxic patients for surgery. Himsworth<sup>6</sup> has confirmed these observations in a series of patients treated with thiouracil, one of the six patients studied by him was operated upon.

In 1942 and 1943, the goitrogenic action of thiocyanate was investigated by members of the Thyroid Clinic of the Massachusetts General Hospital. Observations of thiocyanate goiter in man<sup>7</sup> had led Dr. E. M. Chapman<sup>8</sup> to attempt the use of thiocyanate as a means of altering the thyroid function of four patients with thyrotoxicosis. The results were not encouraging, however, and only one of the four patients treated showed a lowering of basal metabolic rate. Therefore, with the knowledge of Astwood's work, attention was shifted to thiouracil.

The ideal preparative drug for thyroidectomy would be one which so modified the underlying metabolic abnormality as to bring the patient to the surgeon with no evidence of thyrotoxicosis, allowing him to remove the gland and produce permanent relief without subjecting the patient to the hazards of surgery while thyrotoxic. It has been our purpose to ascertain to what degree thiouracil approached this ideal. The complications of thyroidectomy fall into three groups: those related to surgery in general, such as hemorrhage and sepsis, those related to the peculiar anatomical relationships of the thyroid gland, such as nerve or parathyroid injury, and, third, those which stem from the pathologic physiology of thyrotoxicosis, chiefly storm and postoperative thermal reactions. It has been our hope that thiouracil would lessen the hazards in the third group of complications. However, in focusing our attention upon those factors we must not lose sight of possible increased hazards in the first two categories traceable to increased vascularity or friability of the gland.

Thiouracil is a stable organic compound related to thiourea. It is administered by mouth in the form of a 0.1 Gm. tablet, and is well tolerated by the patient with thyrotoxicosis.<sup>1</sup> Toxic by-effects have been observed in occasional cases and will be discussed below, these evidences of toxicity resemble sulfonamide sensitivity, and the same type of precautions should be taken in using thiouracil that one would employ with sulfonamides.

On June 24, 1943, our first thiouracil-treated patient was operated upon, and since that time 53 patients have received the drug as a preoperative measure. Several of these patients received the drug for such a short time as to render observations on its action of little meaning, others were not on the drug at the time of operation or have been followed for too short a time to permit valid conclusions to be drawn. In all, 34 patients have been treated preoperatively, have come to operation on thiouracil, and have been followed long enough to form the basis of this report.

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\* The thiouracil used in this study has been supplied through the kindness of Dr. B. W. Carey of the Lederle Laboratories, Inc.



## CLINICAL DATA

The patients included in this report were seen and diagnosed as having hyperthyroidism by members of the Thyroid Clinic of the Massachusetts General Hospital and by the house and visiting staffs on the wards. The patients prepared for operation with thiouracil were kept in the hospital throughout the period of preoperative treatment. Their response to treatment was followed by basal metabolic rates measured at least twice a week and by the clinical observation of members of the Thyroid Clinic. Unless stated otherwise, the daily dose of thiouracil was 0.6 Gm., usually administered as 0.2 Gm. in three doses. The drug was not started until after a satisfactory base line in basal metabolic rate had been obtained. The drug was stopped on the day of operation. The patients were released from the hospital postoperatively without any medication and are being followed in the Thyroid Clinic.

Eight of our patients had been treated with potassium iodide before thiouracil was started. One continued to take the potassium iodide during the time of treatment with thiouracil. Seven patients had received some form of iodide therapy until 10 to 30 days before starting treatment with thiouracil. They did not receive any further iodine. The remaining 26 patients were previously untreated cases, none of them had received any specific drug therapy for thyrotoxicosis, and thiouracil was the only drug used to alter thyroid function preoperatively.

The patients studied in this series were operated upon by eleven surgeons. Four of the surgeons performed these operations while resident on a surgical service, accounting for 25 of the 34 cases. The remaining nine cases were operated upon by seven members of the visiting staff.\* Unless otherwise specified, the operation performed was a one-stage subtotal thyroidectomy employing section of the strap muscles and hemostasis with fine nonabsorbable suture material (silk or cotton). Drainage for 18 to 24 hours with a small midline or lateral drain was used in several of the cases, it is not routine. The postoperative regimen employs an oxygen tent, intravenous glucose and thiamine, single room and special nurse on all cases. The general handling of the patients follows closely the outline of Cope and Welch.<sup>9</sup>

As a control series, 35 thyroidectomies for thyrotoxicosis, performed at the Massachusetts General Hospital in the years 1941 and 1942, have been selected. These iodine-treated control cases were all operated upon between the months of June and December of their respective years, these being the months during which the thiouracil cases were operated upon in 1943. The distribution of initial B. M. R. levels in this control group of cases coincides closely with that of the thiouracil-treated group. Thus, the 1941 and 1942 iodine-treated cases used here constitute an adequate control group, presenting problems of similar magnitude in their surgical care. These cases, like the thiouracil-treated

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\* We are indebted to Dr. A. W. Allen, Chief, East Surgical Service, Dr. L. S. McKittrick, Chief, West Surgical Service, Dr. J. V. Meigs, Chief, Gynecologic Service, Dr. R. R. Linton, Dr. R. H. Smithwick, and Dr. G. A. Donaldson for data on cases operated upon by them.

TABLE I

I PATIENTS PREPARED FOR OPERATION WITH THIOURACIL ONLY

A—Diffuse Hyperplasia (23 Patients)

Patient No	Age	Sex	Symptoms and Duration	Initial B M R Level	Length of Thio-racil Treatment	Pre-operative Level	Operation	Anesthetic	Nature of Gland	Postoperative Thermal Response	Follow-up Data	Remarks
S M 23895	42	M	Weakness—5 mos	+15	32 days	+5	6 2 1 43	G-O-E	Very vascular—not friable	T 102° Next day Smooth	10 mos —15	
M B 24033	34	F	Palpitation—1 yr Goiter—1 yr Exophthalmos +	+30	16 days	+7	7 15 43	G-O-E	Very vascular and friable		3 mos —10	
E K 24085	20	F	Nervous—3 mos Goiter—2 mos	+38	10 days	+2	7 26 43	G-O-E	Very vascular and friable	T 104° 1st day Smooth	5 mos —11	Operation made more difficult by physical characteristics of gland
J S 24019	30	F	Wt loss—3 mos	+40	17 days	+15	7 31 43	G-O-E	Firm—not very vascular		5 mos +15	
J W 24168	61	M	Weakness—6 mos Exophthalmos +	+20	19 days	±0	9 9 43	Cyclopropane	Vascular—not friable	T 102° 1st day Smooth	5 mos —8	
R R 24218	18	M	Fatigue—7 mos Army rejection	+50	17 days	+22	9 22 43	G-O-E	Soft—hard to handle		9 mos +3	Operated upon prematurely with rate at +22 Preliminary biopsy
B B 422660	53	F	Wt loss—4 mos Exophthalmos ++	+28	17 days	±0	10 22 43	G-O-E	Vascular but firm	Smooth	4 mos —24	Preliminary biopsy
M M 24227	40	M	Wt loss—4 mos	+35	11 days	+10	11 2 43	G-O-E	Soft—not very vascular	T 101° 1st day	3½ mos —26	Preliminary biopsy
F P 24282	21	F	Palpitation—1 mo Goiter—1 mo	+15	17 days (40 days)	±0 —15	11 8 43	G-O-E	Soft—not vascular	T 101°	4 mos +1	Operation postponed because of dental infection, rate then came down to myxedema levels
F D 24336	29	F	Nervous—8 mos Goiter—2½ mos	+60	20 days	+7	11 16 43	G-O-E	Soft—not friable	T 101 8° 1st day	3 mos —13	Preliminary biopsy
L O B 24298	24	F	Nervous—7 mos Diarrhea—6 mos	+35	13 days	+3	12 6 43	G-O-E	Firm—not vascular	T 100° 3 days Smooth	5 mos —10	
J R 24469	53	F	Pain rt eye—9 mos Exophthalmos ++	+45	11 days	+17	1 17 44	G-O-E	Not vascular	Smooth	4 mos —13	Unilateral (right) exophthalmos, not made worse by operation
M G 24472	35	F	Wt loss—12 mos	+25	15 days	±0	1 21 44	G-O-E	Satisfactory	Smooth	2 mos —25	
L A 24361	42	F	Nervous—2 yrs Goiter—1 yr	+45	9 days (30 days)	+5 —2	11 22 43	G-O-E	Firm—not vascular	T 100° 3rd day Smooth	3 mos —26	Preliminary biopsy
B S 24955	15	F	Heat intolerance—3 yrs Treated with x-ray + KI	+35	24 days	+2	1 21 44	G-O-E	Satisfactory		3 mos —7	Off iodine for 3 months before thio-racil started
A B 15207	32	F	Wt loss—9 mos Thyroidectomies 1936—1941	+15	11 weeks	+1	1 22 44	G-O-E	Friable—easy bleeding	Smooth	2 mos +20	Recurrent thyrotoxicosis following 2 operations at outside hospital, treated in Out-Patient Dept for 1st 2 months of thio-racil therapy
J C 24531	10	M	Nervous—1 yr Wt loss—1 yr	+15	31 days	—8	2 24 44	G-O-E	Satisfactory	T 103° 1st day Smooth	2 mos —12	<i>Staph aureus</i> wound sepsis
A K 440001	45	F	Wt loss—1 yr Hypertension	+45	24 days	+15	1 1 44	G-O-E	Satisfactory			Had subsequent lumbodorsal sympathectomy, found to have adenocarcinomatous nodule in gland
R W * 25	25	M	Wt loss—16 mos	+65	26 days	+9	1 18 44	G-O-E	Satisfactory	Smooth		Remarkably dry gland in view of histologic hyperplasia

0.2 Gm per day for last 24 days of treatment

Concomitant treatment with thyroid gr 15 per day did not reduce vascularity

1 mo -22  
1 mo +7

Smooth  
Smooth

Extremely vascular  
Vascular but not friable

G-O-E  
G-O-E

+4  
-1

17 days  
35 days

+35  
+45

Goiter—2 mos  
Nervous—6 mos  
Tremor—6 mos

34 F  
39 F

B—With Long standing Nodular Goiters (3 Patients)

Questionable residual thyrotoxicosis  
Large retrosternal goiter  
Concomitant rheumatic heart disease, with mitral stenosis and auricular fibrillation Did very well post-operatively

6 mos +20  
5 mos -7  
2 wks -10

Smooth  
Auricular fibrillation  
Smooth

Firm but vascular  
Involted—firm  
Involted

G-O-E  
G-O-E  
G-O-E

+20  
±7  
+6

14 days  
20 days  
18 days

+40  
+20  
+28

Goiter—5 yrs  
Nervous—17 mos  
Goiter—15 yrs  
Nervous—6 mos  
Goiter—3 yrs  
Palpitation—3 mos

48 F  
49 F  
43 F

II PATIENTS PREVIOUSLY IODINIZED I PREPARED FOR OPERATION WITH THIOURACIL AFTER STOPPING IODINE TREATMENT (7 PATIENTS)

Palpitation—2 yrs  
Iodine—6 mos  
Wt loss—5 mos  
Taking iodine—1 mo  
Disch from Navy  
Nervous—15 mos  
Goiter—15 mos  
On iodine—1 yr  
Soreness of eyes—10 mos  
Wt loss—4 mos  
On iodine 1½ yrs  
Exophthalmos + + + +  
Nervous—18 mos  
On iodine—3 mos  
Weakness—8 mos  
Iodine—8 mos  
Dyspnea—7 mos  
Iodine—5 mos

+30  
+40  
+30  
+35  
+30  
+50  
+55  
+25

19 days  
29 days  
14 days  
27 days  
14 days  
35 days  
35 days  
20 days

Well involuted—firm  
Soft—friable hemorrhagic  
Soft—not smooth friable  
Firm—not vascular

G-O-E  
G-O-E  
G-O-E  
G-O-E

+16  
+12  
-8  
-5

6 mos +9  
2 mos +11  
5 mos -26  
3 mo- +7

T 102°  
T 103°  
Smooth  
T 101°

1st day  
3 days  
Smooth  
1st day

51 F  
18 M  
39 F  
39 M

Done in two hemithyroidectomies Prepared for first side with iodine  
Severe ophthalmopathy, not made worse by thiouracil or operation On thyroid gr 3 a day for 4 months

4 mos -31  
2 mos -5  
2 mos -5

Smooth  
T 101°  
Smooth

Soft—not friable  
Firm—vascular  
Firm—not vascular

G-O-E  
G-O-E  
G-O-E

+2  
-8  
+2

31 days  
35 days  
20 days

+25  
+25  
+25

Nervous—2 yrs  
On iodine—3 mos  
Exophthalmos + + + +

28 M

III PATIENTS PREPARED FOR OPERATION WITH IODINE AND THIOURACIL (1 PATIENT)

Preliminary pole ligation  
minimal lowering of rate by thiouracil—Iodine given simultaneously

9 mos +23

Smooth

1 mm

Iodine

+20

31 days

+25

Nervous—2 yrs  
On iodine—3 mos  
Exophthalmos + + + +

28 M

\* Patient of Dr L S McKittrick, Palmer Memorial Hospital

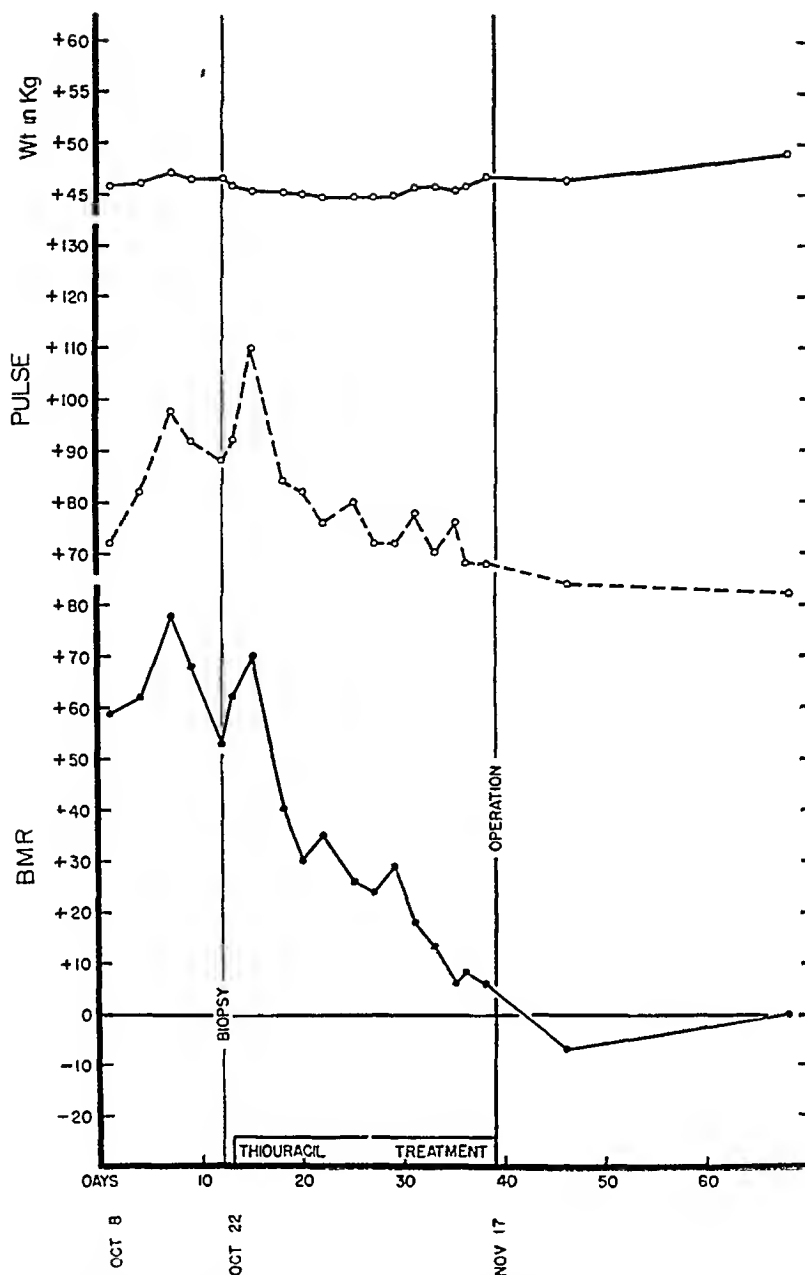


FIG 1—Pulse, weight and BMR responses of patient F D (No. 24336) to thiouracil treatment, a previously untreated case of hyperthyroidism with an initial BMR "level" of +60. The drug was started following biopsy of the gland. The rate rapidly fell to the neighborhood of +5, at which point subtotal thyroidectomy was performed. The pulse response is striking. There was no significant weight gain in this case. The histologic appearance of the thyroid at biopsy and at thyroidectomy is shown in Figure 8.

patients, were operated upon in the great majority of instances by the surgical residents. The postoperative handling was identical with the exception of the fact that the thiouracil cases received no postoperative iodine.

The clinical response to thiouracil was satisfactory in all of our patients. The patients experienced improved tolerance for the heat, decreased nervousness, and increased strength usually within ten days of starting the drug. The tremor was observed to decrease and to disappear in several cases, and the pulse rates became nearly normal. The weight curves were variable.

The thyroid glands did not appear to become larger, nor did they become firmer, as one usually observes in the thyrotoxic patient treated with iodine.

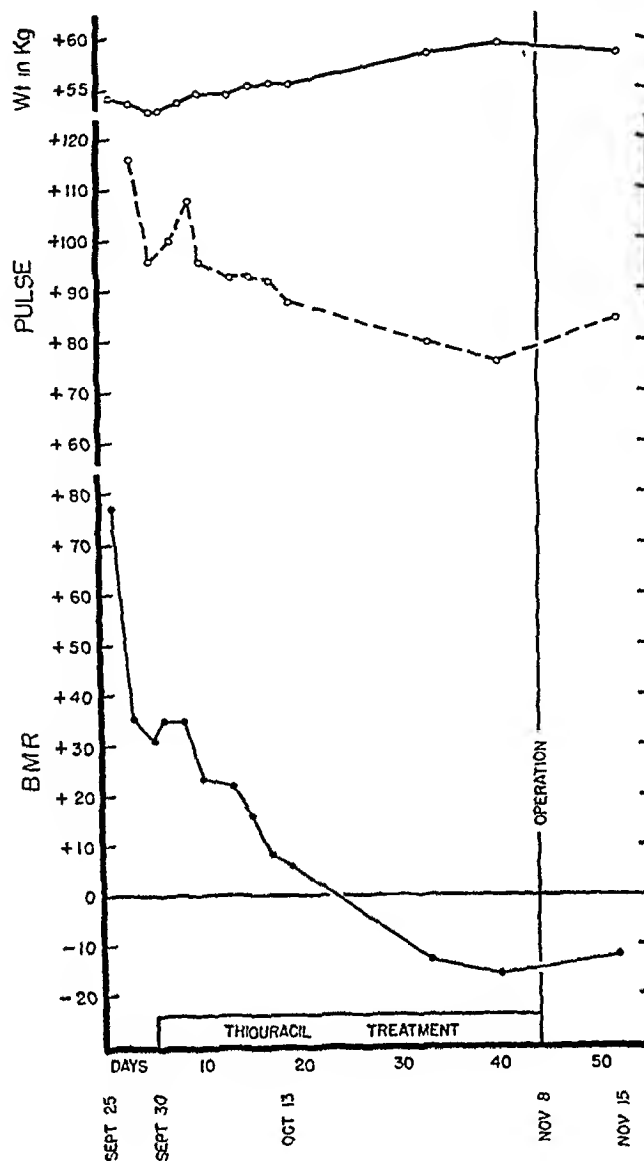


FIG. 2—Pulse, weight, and B M R responses of patient T P (No 24282) to thiouracil treatment. With an initial B M R of +78, settling down on bed rest to a "level" of +35, this patient's B M R fell to +0 in 17 days of treatment. Further treatment was necessitated by the appearance of dental sepsis which postponed operation, in a total of 40 days of treatment the B M R fell to -16 and the patient became clinically myxedematous (compare with histologic sections shown in Figure 11)

Indeed, in a few cases the thyroid became softer. This change in consistency gave the impression in some instances that the gland became smaller. A bruit and thrill appeared over the thyroid in several cases. In no instance did a pre-existing bruit disappear during treatment with thiouracil. In some patients the bruit became louder, an observation which correlates with the vascularity observed at operation and seen on microscopic section.

#### THE PREOPERATIVE BASAL METABOLIC RESPONSE

The basal metabolic response to thiouracil is signalized by the fact that it is evidently possible to bring the rate down to between 0 and +10 regardless

of the initial values, providing one maintains treatment with the drug for an adequate period of time

The initial fall in basal metabolic rate in the cases treated with thiouracil alone is similar to the iodine response curves reported by Means and Lerman<sup>10</sup> In contrast to the iodine response curves which level off after an initial drop the thiouracil response curves continue their descent until a myxedema level is approached A series of curves showing the metabolic response to thiouracil is presented in the paper by Rawson, *et al*,<sup>11</sup> reporting the metabolic studies with thiouracil carried out in this clinic

The basal metabolic responses seem to fall into two groups In the patient with untreated thyrotoxicosis, having an initial basal metabolic rate in the higher range and with diffuse hyperplasia, the response to thiouracil is usually rapid and the fall to a normal metabolic rate may take place within ten days to three weeks Examples of this type of response are shown in Figures 1 and 2

Patients treated with iodine before thiouracil therapy constituted a second group The fall in the basal metabolic rates of these iodimized patients was delayed as compared with the fall noted in the basal metabolic rates of previously untreated cases, requiring from four to six weeks to reach normal

One patient who was fully iodimized was treated for a month with thiouracil, continuing iodine during this period The response to this therapeutic combination was minimal and during the month in question his rate did not significantly depart from a level of  $+20$  We realize, in the light of subsequent experience, that the response would have been more rapid had iodine treatment been discontinued, or, conversely, had we elected to continue iodine, we should have been content to wait two or three months for the thiouracil response \*

Two patients who had had large goiters for many years and had only recently developed symptoms of thyrotoxicosis were also slow in their response to thiouracil The histologic appearance of their thyroids was that of involution with secondary hyperplasia Clinically and histologically, they tend to fall in the same group as those patients who had received iodine treatment before thiouracil was started An example of this group is shown in Figure 3

It is our conviction at the present time that if thiouracil is continued, however, even in this group of iodine treated patients or patients with old nodular goiters recently become toxic, ultimately a complete metabolic response will be obtained During the course of our work we were not aware of this fact in some of the earlier cases and doubtless operated upon them prematurely from the standpoint of the basal metabolic response

In Table I are shown the essential data on all the operated cases, divided into groups according to their status with respect to iodine therapy

#### COMPARISON WITH IODINE-TREATED CASES

Any attempt to evaluate thiouracil preparation must involve a comparison with the previous method of preparation which it may replace In an effort

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\* A patient who did not come to operation on thiouracil because of a failure to demonstrate a metabolic response to the drug during six weeks of treatment with both thiouracil and iodine also demonstrates this point

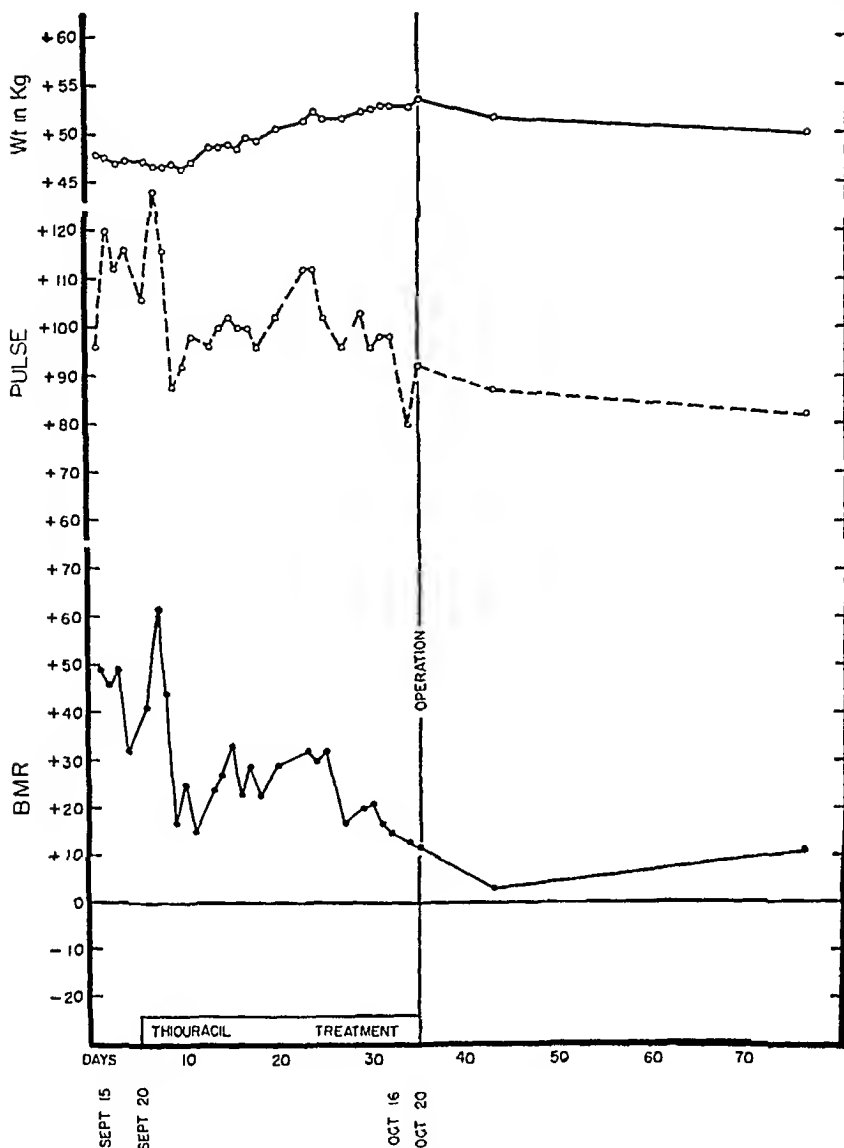
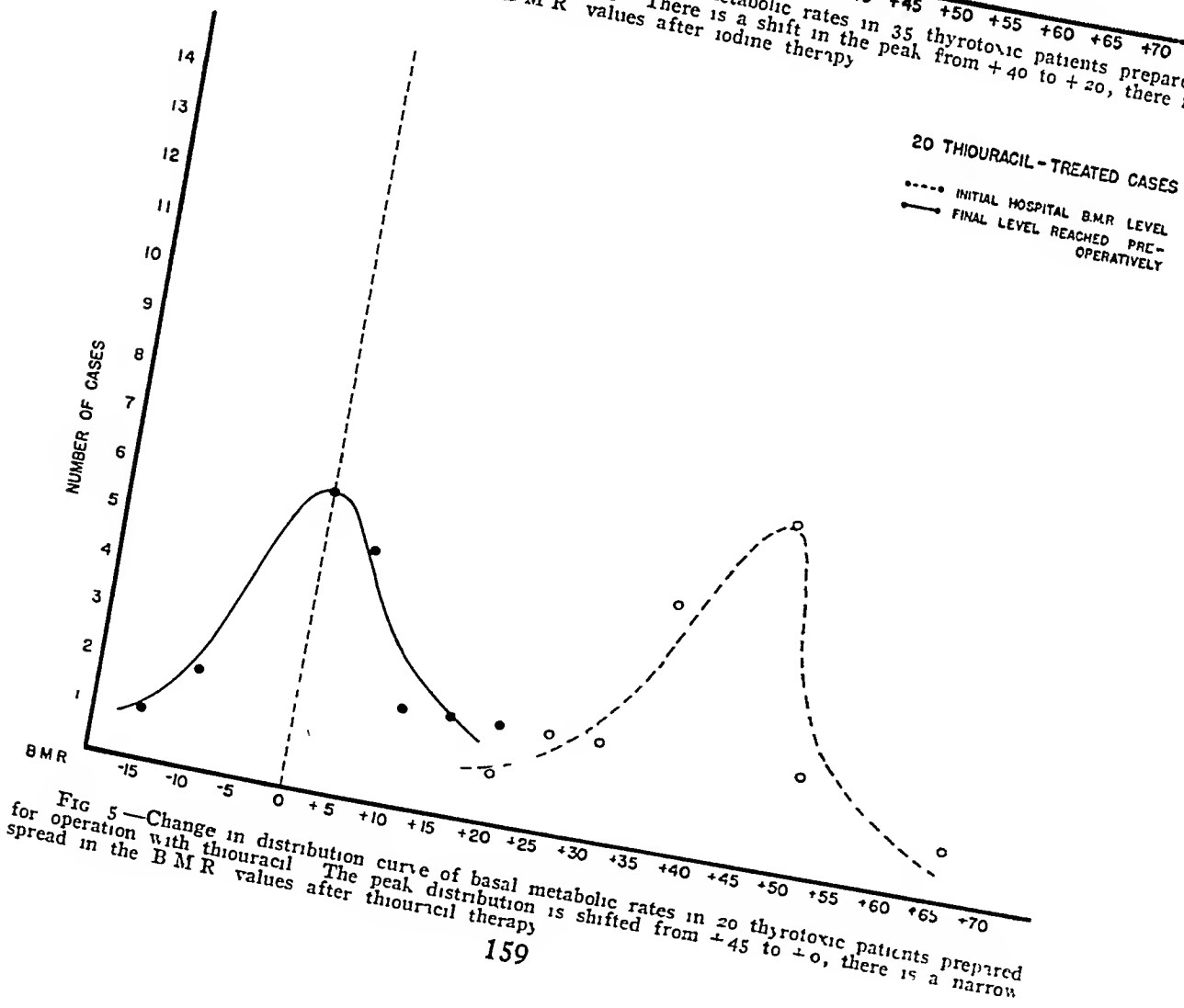
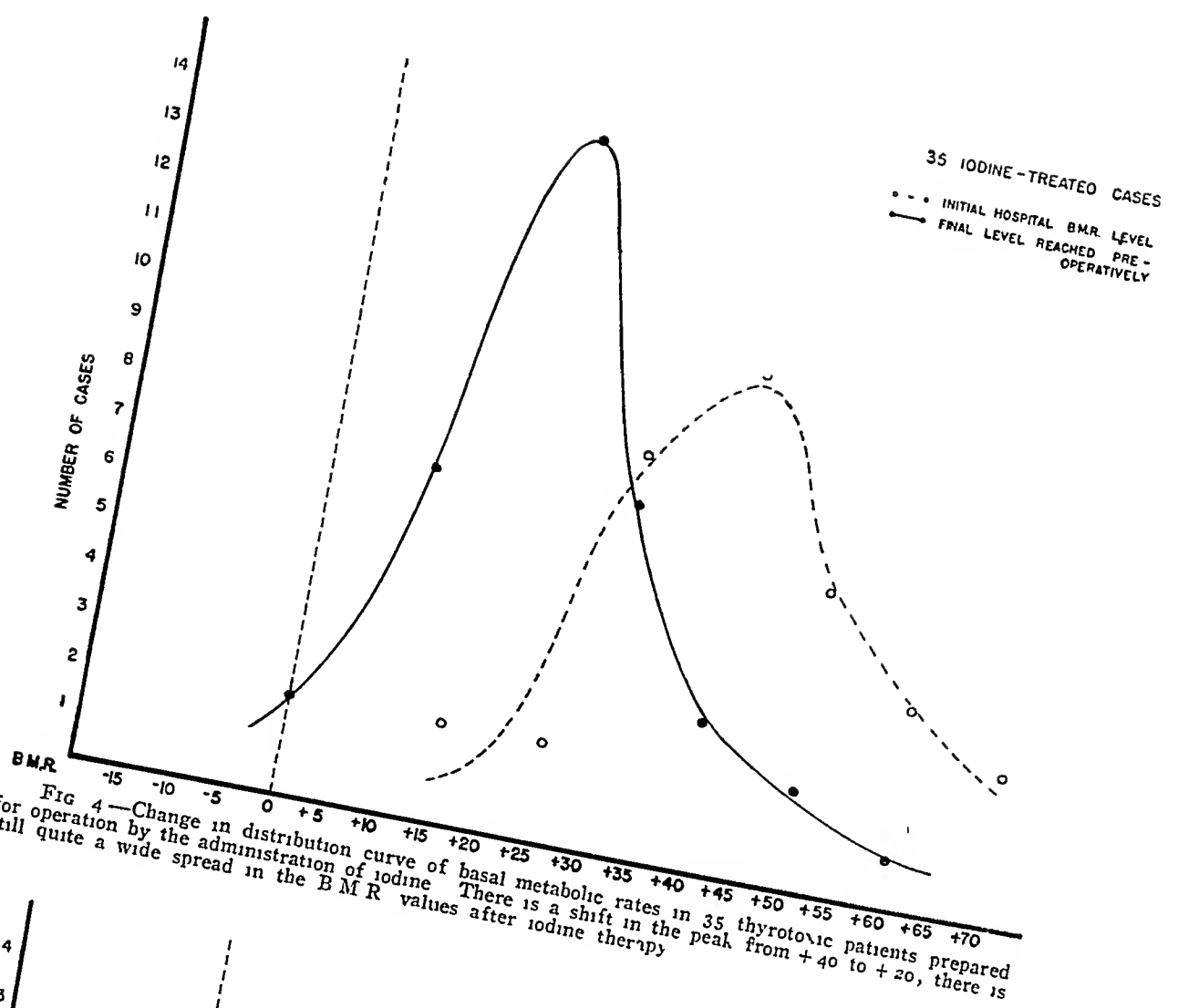


FIG 3—Pulse, weight, and BMR responses to thiouracil of a patient (M B No. 24180) with a long-standing colloid goiter recently become toxic. Treatment for 30 days did not alter markedly the trend of the BMR. In retrospect, we realize that this patient was operated upon prematurely, and that another 10 or 15 days of treatment might have sufficed to reduce the rate to normal. Compare with histologic sections (Figure 13).

to accomplish this, 35 thyroidectomies performed with iodine preparation have been analyzed with respect to their preoperative metabolic response and postoperative course.

The preoperative metabolic response to thiouracil differs strikingly from iodine preparation in one important regard which it is difficult to overemphasize. This difference resides in the fact that a group of iodine-treated cases show a shift downwards in their metabolic rate, averaging about 25 points, whereas thiouracil treatment shifts the distribution of metabolic rates from the same starting figure to the region of  $\pm 0$ , a drop of almost 50 points.

As shown in Figure 4, the iodine-treated patients show a shift in the peak distribution from a B M R of  $+45$  to a B M R of  $+20$ , but there is a very considerable spread, with some of the patients after iodine therapy still main-





taining a B M R in the higher level, with others falling quite low. On the other hand, as shown in Figure 5, the thiouracil group show a shift in peak from  $+45$  to  $\pm 0$ , and the cases are rather closely grouped between 0 and  $+10$  at the preoperative determination. Stated otherwise, thiouracil, if correctly used, can be relied upon to bring the patient's metabolic rate to or near 0 before operation. The iodine response curves of Means and Lerman<sup>10</sup> demonstrate that with a peak distribution of initial B M R's at  $+40$  one will naturally expect the level to be  $+20$  after iodine therapy. Furthermore, we know from experience that if the iodine is continued on for another two or three weeks, the level will usually not fall much lower. With thiouracil the level will continue to fall until it reaches  $\pm 0$  or lower.

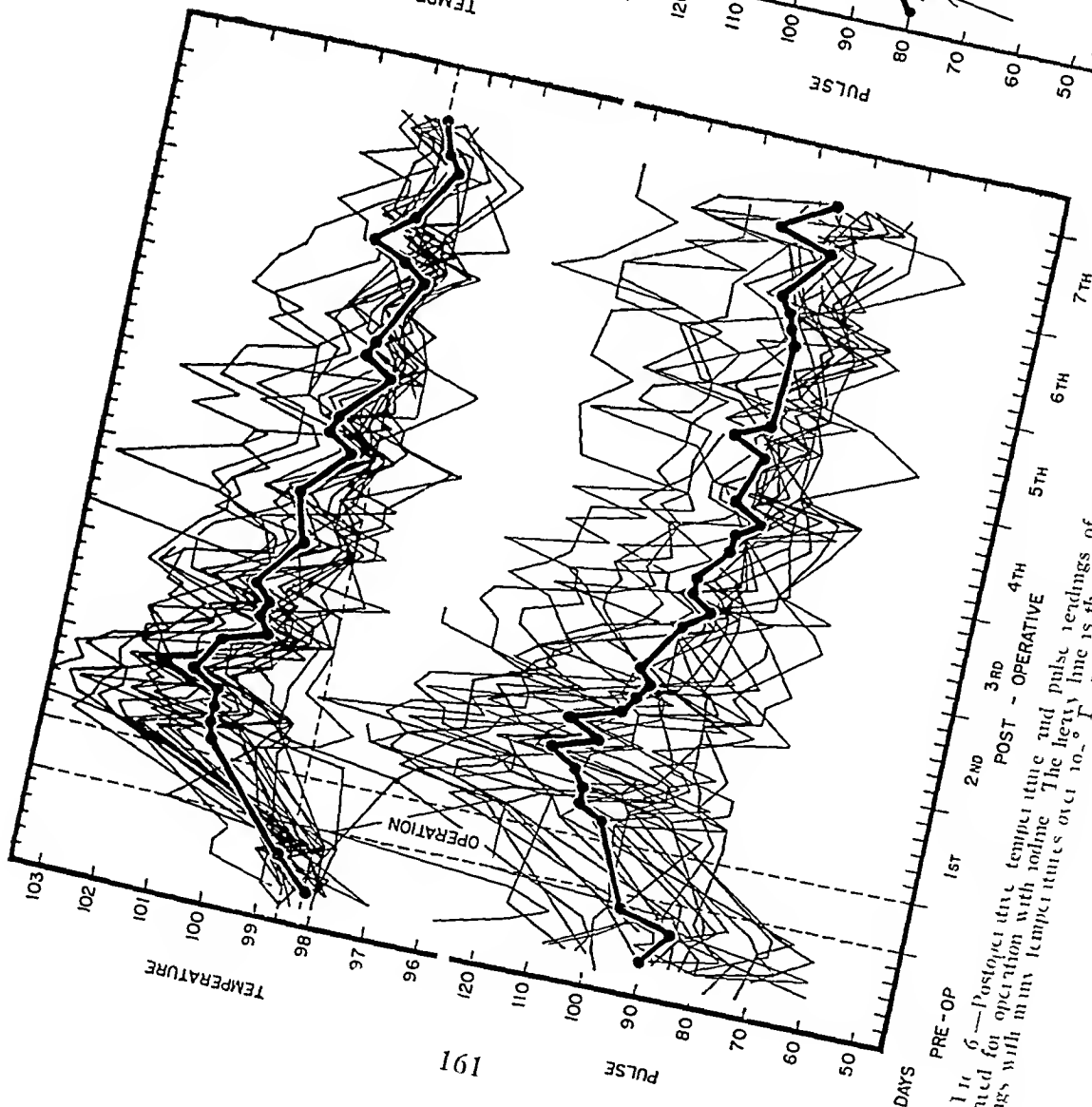
It is probable that continuance of thiouracil over a period of months will produce myxedema in thyrotoxicosis, two thyrotoxic patients treated by us have been allowed to fall to levels in the vicinity of  $-15$  before operation. Furthermore, we know from one case seen in this clinic that thiouracil given in adequate doses over a period of months can produce a large goiter and clinical myxedema in a nonthyrotoxic patient. In the surgical cases, operation has usually been performed with the rate in the vicinity of 0 to  $+10$ , at which time the drug has been stopped.

For those clinicians who feel that an iodine "escape" phenomenon may occasionally complicate prolonged preoperative iodine treatment, thiouracil has the advantage that long-continued treatment serves always to lower the B M R further, as shown in Figure 2. This patient, ready for operation after 17 days of treatment, could not be operated upon because of oral sepsis. A further 23 days of treatment only served to lower the rate further, finally producing clinical myxedema at which point the patient was operated upon.

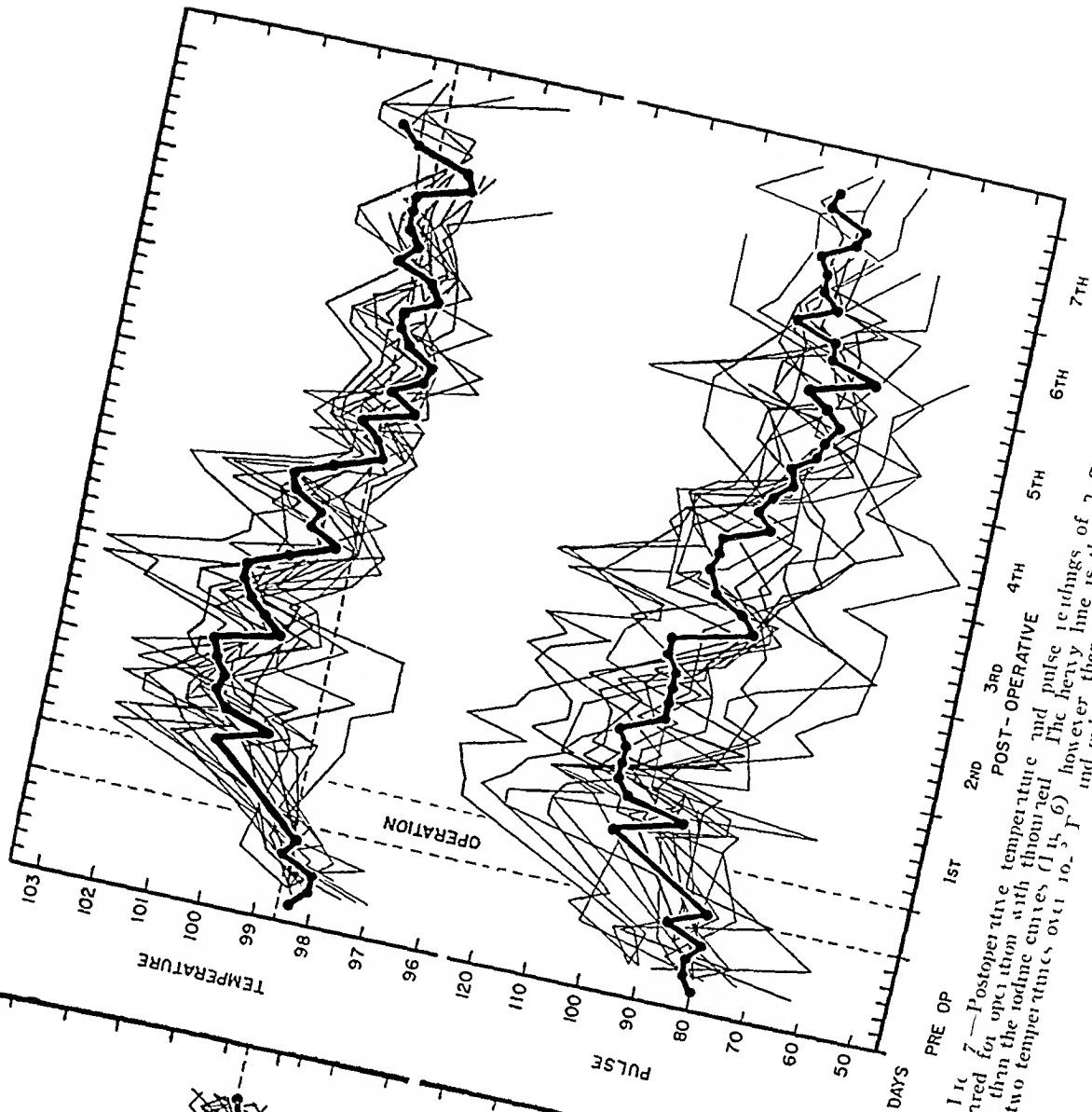
#### OPERATIVE AND POSTOPERATIVE CHARACTERISTICS OF THE THIOURACIL-TREATED PATIENT

As has been pointed out previously, some of the glands show an unusual degree of hyperplasia histologically and a grossly increased vascularity after thiouracil preparation. In an occasional patient the vascularity may be sufficiently exaggerated to hamper the surgeon and complicate the operation. This phenomenon was of surgical significance in three of the 34 operated cases.

The operative course of this group of patients was satisfactory from the standpoint of pulse and blood pressure responses. Indeed, in many instances the even pulse and blood pressure readings over a two-hour period were quite striking and most unexpected for the degree of thyrotoxicosis existing previous to treatment. The intra-operative blood pressure and pulse response has been used<sup>9</sup> by the resident surgeons of this hospital for some time as one of the chief criteria in selecting hemithyroidectomies as the surgical treatment for any given case. In this group of thiouracil-treated patients none required hemithyroidectomies for this reason. One patient prepared for her first operation with iodine (B K No 24323)



116 6—Postoperative temperature and pulse readings of 1 group of thyrotoxic patients prepared for operation with iodine. The heavy line is the average, there is a wide spread in the readings with many temperatures over  $100^{\circ}\text{F}$ , and many pulse rates over 120



117 7—Postoperative temperature and pulse readings of 1 group of thyrotoxic patients prepared for operation with thyroidal. The heavy line is the average, and is not significantly lower than the iodine curves (116, 6) however there is much less variation in the readings with only two temperatures over  $100^{\circ}\text{F}$  and only one pulse rate consistently over 120

necessitated hemithyroidectomies and was prepared for her second operation with thiouracil. Another patient (M. S. No. 23309) was selected for hemithyroidectomies preoperatively because of the presence of a large iodine-fast goiter and the development of a leukopenia while on thiouracil. Actually her operative response during the first operation was entirely uneventful.

Charts showing the postoperative response of the thiouracil group as compared with the control group of cases are shown in Figures 6 and 7. In Figure 6 is shown the postoperative temperature and pulse readings for a group of iodine-treated thyrotoxic patients. There is a wide spread in the readings, with many temperature readings over  $102^{\circ}$  F. and many pulse rates over 120, some up to 160. The average shown by the heavy line is not excessive in either respect. The thiouracil-treated postoperative cases are shown in Figure 7. Here the average temperature curve is not significantly lower than in the iodine cases. The pulse average is lower however, barely going over 100 where the iodine-treated group shows an average over 100 for a 24-hour period. In the case of both temperature and pulse readings the spread is much less in the thiouracil cases. Only two temperatures rise over  $102^{\circ}$  F. and these both on the second day, due to minor degrees of atelectasis, not on the basis of thyrotoxicosis. Only one pulse stays over 120 for several readings.

The postoperative course of the thiouracil-treated patients has been smoother than that we have become accustomed to expect following the preoperative preparation with iodine. The course has been more disturbed than in patients following resection of a nontoxic goiter, however, as evidenced by frequent temperature readings between  $100^{\circ}$  F. and  $101^{\circ}$  F. on the first and second postoperative days.\*

It is apparent therefore that though the metabolic rate is reduced to normal by the thiouracil, the entire physiologic status of the patient is not in equilibrium; the autonomic nervous system is still to some degree disturbed. This is a manifestation of the fact that though thiouracil inhibits the formation of thyroid hormone, it does not affect the underlying etiologic mechanisms of thyrotoxicosis; this fundamental autonomic imbalance persists and may be responsible for the residual postoperative thermal responses seen in many of our cases.

#### HISTOLOGIC AND METABOLIC OBSERVATIONS

The surgically-removed thyroid glands when examined histologically showed in contrast to the involution observed in iodimized thyroids, hypertrophy or marked hyperplasia with diminished or absent colloid. In view of this hyperplasia and in view of the marked hyperplasia observed in the experimental goiters produced in animals by the administration of thiouracil, a very natural question presents itself: "Does the administration of thiouracil

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\* One patient developed paroxysmal auricular fibrillation postoperatively. She had a large retrosternal gland, and manipulation in the anterior mediastinum was necessary in order to remove it. The fibrillation was controlled by quinidine and digitalis, and might have been prevented by the preoperative use of these agents.

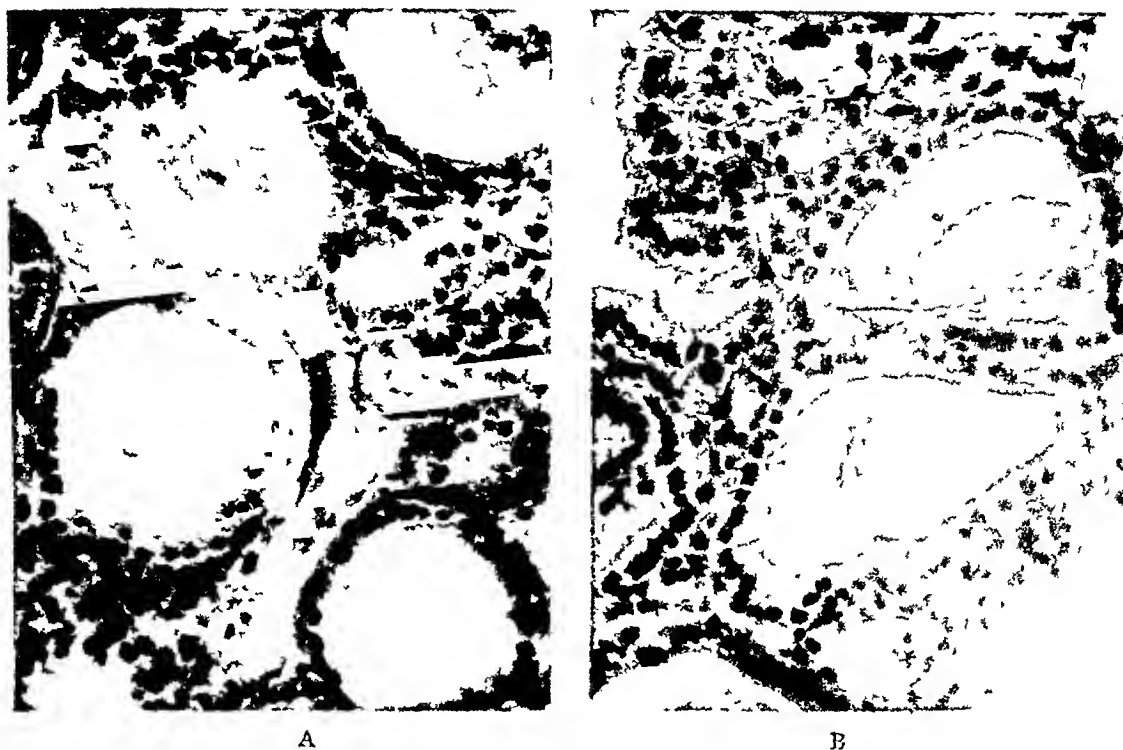


FIG 8—Sections of thyroid from patient F D (No 24336) taken (A) before initiating thiouracil treatment, and (B) after 20 days of treatment. The acinar cell height has been increased an average of 4.2 micra.

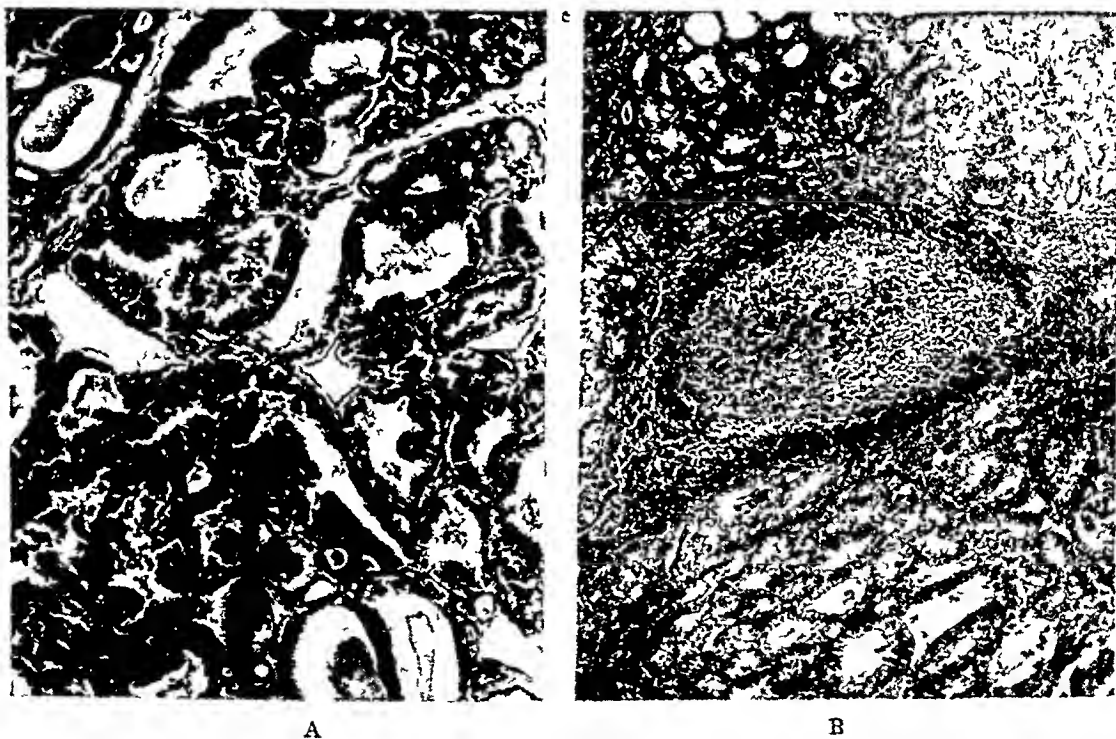


FIG 9—Section of thyroid from patient B B (No 422660) taken (A) before starting thiouracil treatment, and (B) after 17 days of therapy. The normal structure of the thyroid has been partially replaced by lymphoid tissue and the remainder shows extreme hyperplasia.

in hyperthyroidism increase the already existent thyroid hypertrophy and hyperplasia?" With this question in mind, biopsies were done on the thyroids of five patients before thiouracil therapy was started. The histologic picture of the biopsy specimen was compared with the histologic appearance of at least four different areas from the glands removed at operation.

These preparations were examined under oil immersion and the height of one representative cell from each of 100 successive acini was determined in each slide. Some increase in the mean acinar cell height was observed in the thyroids of all patients studied, indicating increased hyperplasia in the thiouracil-treated glands. In one patient the increase in mean cell height averaged 4.2 micra (Fig 8). In another patient the biopsy showed only hypertrophy and hyperplasia, several specimens of the surgically removed thyroid examined after treatment with thiouracil showed in addition to the hypertrophy and hyperplasia of the acinar cells hyperplasia of lymphoid tissue. In several areas (Fig 9) the acinar structure of the thyroid was almost completely replaced by lymph follicles.

The most prompt clinical and B M R responses were observed in those patients whose thyroids on histologic examination showed marked hyperplasia and practically no stored colloid. As an example, a 20-year-old girl (E K No 24085), who had classic exophthalmic goiter of moderate severity, showed a basal metabolic rate before starting treatment of +38. Clinical improvement was rapid on thiouracil, and by the tenth day of therapy the metabolic rate had fallen to +2. The histologic picture of the resected thyroid, shown in Figure 10, was that of marked hyperplasia with almost complete loss of colloid.

A further example of this phenomenon is shown by another 20-year-old girl (F P No 24282) who on admission to the ward appeared extremely toxic. With bed rest and sedation she improved. Her B M R level before starting treatment with thiouracil was +35. She made a good response to thiouracil and in 17 days her metabolic rate had fallen to +7. The evening before scheduled operation she developed a fever which was due to two dental abscesses. Thiouracil administration was continued, the dental abscesses were drained, and the infected teeth removed. Within 30 days the metabolic rate had fallen to -16 and the patient appeared to be myxedermatous. Operation was performed on the 40th day of thiouracil treatment. Her thyroid was found to be so hyperplastic that in some parts of the gland the acinar structure was completely replaced by columns of epithelial cells, as shown in Figure 11. In this patient, after 40 days of therapy, clinical myxedema coexisted with extreme histologic hyperplasia.

In contrast, is the example of an 18-year-old male (W L No 24260) admitted to the hospital wards with moderately severe thyrotoxicosis, and a B M R level of +40. He made a slow response to treatment with thiouracil. The B M R fell to +12 in 30 days. The thyroid (Fig 12) even after treatment was found to be involuted with practically no hyper-

# THIOURACIL IN THYROIDECTOMY



FIG 10

FIG 10—Sections of thyroid removed from patient L K (No 24038) after ten days of thiouracil treatment. There is virtually complete loss of colloid in an extremely hyperplastic gland.



FIG 11

FIG 11—Histologic section of thyroid gland from patient T P (No 24282) after 40 days of thiouracil treatment. Although the histologic appearance is that of extreme hyperplasia, the B M R was -16, and the patient clinically myxedematous.



FIG 12

FIG 12—In contrast to the previous photomicrographs, this section from the thyroid of patient W L (No 24260) shows the appearance of an iodimized thyroid following 30 days of treatment with thiouracil. It is evident that involution still predominates with only slight superimposed hyperplasia.

FIG 13—Microscopic appearance of a long standing colloid goiter, recently become toxic, after 22 days of thiouracil treatment (Pt M B, No 24273). As in the iodimized gland involution predominates.

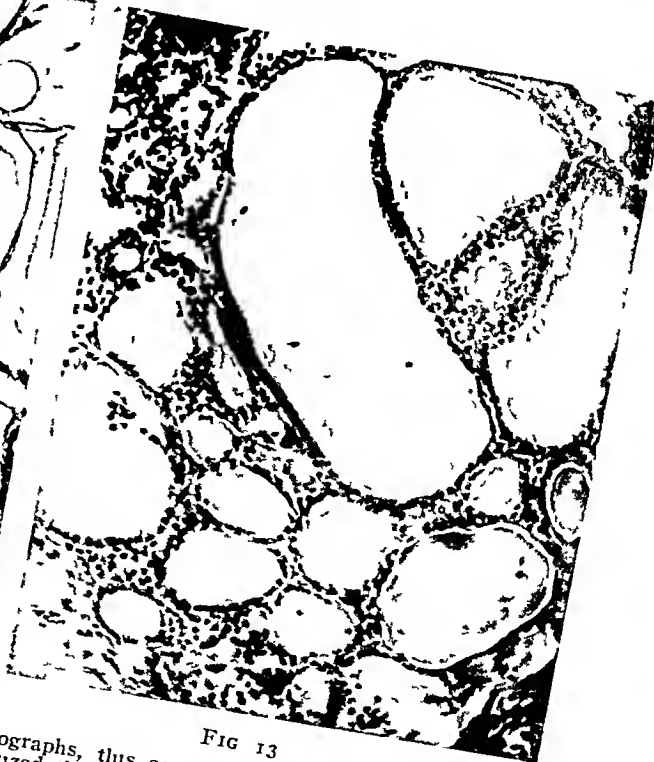


FIG 13

plasia, a fact difficult to reconcile with our other experiences with untreated cases. After the thyroid sections had been examined the patient was again asked about previous therapy, and he then admitted having taken iodine for several weeks before admission to the hospital. This disclosure of previous iodization explained the apparently incongruous findings.

Also in contrast, a 49-year-old housewife (M. B. No. 24273) entered the hospital for treatment of palpitation. She had had a large goiter for 15 years, and had had mild symptoms of thyrotoxicosis for five months. She had a B. M. R. level of  $+20$ . After 22 days of treatment with thiouracil the basal metabolic rate fell to  $+7$ . The operatively removed thyroid examined histologically revealed involution with little hyperplasia, as shown in Figure 13.

Astwood<sup>7</sup> has advanced the theory that thiouracil acts by preventing the completion of physiologically active hormone and that it does not affect the preformed hormone. Our observations that the most rapid clinical and B. M. R. responses to thiouracil treatment were observed in those patients whose thyroids originally showed hyperplasia and practically no colloid, support Astwood's theory.

In ten of the patients who had been prepared for thyroidectomy with thiouracil the uptake of radioactive iodine (eight-day half-life) was studied. Each of these patients was given a tracer dose of radioactive iodine (150 micrograms of iodine as sodium iodide) 24 to 48 hours before operation. All of the urine excreted from the time of radioactive iodine administration to the time of operation was collected in 24-hour amounts. The per cent of radioactivity excreted in the urine then was determined, as well as the amount of radioactive iodine contained in the thyroid at the time of operation. In general, it was observed that most of the administered iodine was excreted in the urine and that very little radioactivity was demonstrable in the thyroid tissue.<sup>11</sup> This is in distinct contrast to the reported<sup>12</sup> findings in untreated thyrotoxicosis and lends considerable support to Astwood's theory; it suggests further that the "block" in elaboration of hormone takes place at the level of iodization.

#### TOXICITY

Thiouracil appears to exhibit a degree of toxicity similar to the less toxic sulfonamides whose toxic properties it resembles. Amongst 52 patients treated to date we have observed two leukopenias, four oral infections possibly related to the drug, and a generalized lymphadenopathy which cleared after stopping the drug at operation. Dr. Astwood\* has observed a leukopenia while treating a patient with 2.0 Gm per day and four drug fevers. Drug fever and rash have been reported in the literature, in two of our patients the development of a fever was associated with sensitivity to the drug as manifested by an abrupt rise in temperature to  $103^{\circ}$  F after a single dose of thiouracil, following a few days' cessation of dosage.

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\* Personal communication from Dr. E. B. Astwood.



The leukopenias observed in two of our patients involved a fall in white count to the neighborhood of 2500, the percentage of polymorphonuclear leukocytes never fell below 30 per cent. In one patient the drug was continued with return of the count to normal. In another, the drug was stopped. The dental infections and gingivitis observed in two patients involved postponing operation but did not alter the outcome of treatment.

In no case has any toxic manifestation either complicated operation or involved abandonment of surgery. In the two patients who developed drug sensitivity, with fever, preoperative preparation was completed with iodine. Because these two patients did not come to operation on thiouracil they are not included in Table I.

#### COMMENT

Thiouracil changes profoundly the function of the thyroid gland. The experimental observations and the initial clinical observations of Astwood with this drug have been amply confirmed. The place of the drug in the treatment of hyperthyroidism, however, has not been settled finally.

At the Massachusetts General Hospital we have reserved the drug in nearly all instances for the preparation of patients for thyroidectomy. As such it is more effective than iodine or any other previously tried agent or combination of methods. If used correctly, the metabolic rate of the patient is reduced to normal or lower. From the point of view of metabolic rate the operative risk, therefore, is apparently that of the patient with nontoxic goiter. Both the operative and postoperative courses of the patient who has been prepared with this drug are less tempestuous than the patient prepared with iodine, in whom there is usually a residual elevation of metabolic rate. It should be pointed out, however, that in a few patients, even though the basal metabolic level was well within normal limits immediately before operation, there were upheavals of cardiac function and rises of body temperature after operation reminiscent of the patient operated upon with active hyperthyroidism. Although clinical improvement paralleled the drop in metabolic rate, the entire physiologic state had not returned to normal. This may indicate that thyrotoxicosis is essentially a biphasic disorder—one phase the result of cellular metabolic changes produced by thyroid hormone in excessive amounts, and the other phase a more fundamental etiologic process related either to the pituitary or autonomic nervous system, or both. Thiouracil can alter only the metabolic phase of the disease (by blocking the iodination of the hormone) leaving the underlying autonomic or endocrine disorder unchanged. It is this latter aspect of hyperthyroidism which must be approached in future therapeutic endeavors and which at present produces some postoperative upheaval in the patient prepared with thiouracil.

Since the usefulness of the drug as far as operation is concerned lies in the reduction of the metabolic rate to normal, it is unfortunate that those patients needing the drug the most, the thyrocardiacs, are the ones in whom



the drug takes the longest to act. The thyrocardiac represents the patient carrying the worst surgical risk. These are usually patients in the older age-group, in whom the limited cardiac reserve of age has been completely absorbed by the excessive cardiac load of thyrotoxicosis and in whom, therefore the added burden of operation is prone to initiate serious decompensation. Such patients have often had long-standing, well involuted goiters. The colloid presumably stored in these glands delays the clinical effectiveness of thiouracil. Several weeks or a month of therapy, with the patient bedridden, may be needed before improvement is adequate for operation. The advantages of the drug, however, outweigh the disadvantages of prolonged preparation unless the patient's toxicity is very mild. In any case selected for treatment the drug should be started and no considerations short of frank toxicity should dissuade the clinician from continuing it until the full benefit is obtained and the B. M. R. is at 0 or below.

Knowing that Doctor Astwood and others were centering their attention on the possible medical cure of hyperthyroidism with thiouracil, this clinic has treated but few cases with thiouracil and without surgery. It is perhaps unwise to compare at this stage his observations with ours, but certain pathologic and physiologic considerations in regard to the eventual medical therapy of hyperthyroidism with this drug are of importance at present. Thiouracil is goitrogenic, given to one patient in the absence of hyperthyroidism it produced an acute hyperplastic goiter similar to that encountered in a patient following thiocyanate therapy. Thiouracil also increases hyperplasia in the patient suffering from hyperthyroidism. From an anatomic point of view therefore, it enhances the primary anatomic change of the disease. Iodine in contrast reverses the disease anatomically by inducing involution. An anatomic reversal similar to that of iodine would seem more likely to produce permanent relief as a means of medical treatment.

Ideally, having blocked the formation of thyroid hormone with thiouracil, it would be advantageous to produce regression of the resultant anatomical changes by the use of thyroid or iodine as a preliminary to operation. This has not been done in enough cases, as yet to permit a report as to its usefulness.

In recurrent thyrotoxicosis one must bear in mind that the increased vascularity of the gland may be especially troublesome, working in a scarred field. In any case the surgeon must use care and caution in his operation as the hyperplasia and vascularity of the gland may render a hurriedly done procedure unnecessarily bloody.

#### SUMMARY AND CONCLUSIONS

1. Thiouracil has been administered to 53 thyrotoxic patients as a preparation for thyroidectomy. Of these 34 have come to operation and been followed long enough to form the basis of this study. Of these 34, 26 have received thiouracil as the only preparative drug.

2. Thiouracil is superior to iodine as a preparation for thyroidectomy.

because, regardless of the degree of elevation of the metabolic rate prior to therapy, it will bring the patient to operation with a normal metabolic rate

3 The histologic change accompanying this lowering of the basal metabolic rate is an intensification of the hyperplasia seen in thyrotoxicosis. Thiouracil produces an hyperplastic but nonfunctioning goiter.

4 An occasional disadvantage of the use of thiouracil in preparing patients for surgery lies in the fact that this hyperplasia is accompanied by an increased vascularity and friability which makes the gland more difficult to handle and renders hemostasis arduous.

5 The increased vascularity is especially troublesome if the patient has had a previous thyroidectomy.

6 Preliminary, or concomitant, iodine administration delays the thiouracil response, it is possible but not yet proven that iodine therapy subsequent to thiouracil treatment may play a useful role in reducing hyperplasia and vascularity.

7 Toxicity not unlike that of the sulfonamides may be expected to occur when treating patients with thiouracil.

8 Thiouracil, while an improvement over iodine as a means of preparing patients for surgery, is not yet the ideal drug for this purpose because it increases the histologic abnormality of the disease, because it affects only the production of hormone and not the underlying etiology of hyperthyroidism, because surgery may be rendered more difficult by it, and because disturbing evidences of toxicity may become manifest.

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# SUBTOTAL GASTRECTOMY FOR DUODENAL ULCER\*

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IT IS INEVITABLE in the treatment of any disease that certain progressive changes are bound to occur with the accumulation of experience. On July 1, 1937, a new group of surgeons was delegated to care for ward patients suffering from peptic ulcer. In the course of the ensuing six years, certain modifications were gradually evolved in preoperative management, anesthesia, operative technic and postoperative care. The ultimate aim of these innovations was the diminution of the morbidity and mortality incident to the surgical therapy of duodenal ulcer. In an effort to determine the efficacy or failure of these changes, a detailed study was made of the records of all ward patients upon whom a subtotal gastrectomy was performed for duodenal ulcer. It was possible for comparative purposes to divide these cases into two series. Series A 79 patients (July 1 1937 to June 30, 1940), and Series B 94 patients (July 1, 1940 to June 30, 1943).

It is granted that duodenal ulcer, in its incipency is not a surgical problem. It only becomes one when certain complications occur which do not respond to medical therapy. These are, excluding acute perforation, the failure of repeated medical "cures" to relieve persistent pain, severe and recurrent hemorrhages, and intractable pyloric or duodenal stenosis. All patients in this series presented one or more of these complications but no patient was operated upon without the approval of an internist or gastro-enterologist.

## HISTORY

The ulcer symptoms had been present in the majority of patients for many years. This is readily appreciated in reviewing Table I.

TABLE I  
DURATION OF DISEASE

Approximate years duration	5 years	5 years	10 years	15 years	20 years
Number of cases	55	51	34	21	14

The chronicity of the disease may be seen by a brief statistical study of the symptomatology listed in Table II.

This series of 173 cases was further divided, mainly on a basis of the history, into the following three groups

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\* Read before The Surgical Section New York Academy of Medicine, May 5, 1944

# GASTRECTOMY FOR DUODENAL ULCER

TABLE II  
SUMMARY OF IMPORTANT FACTS IN HISTORY

Intractable pain	156
One or more episodes of hemorrhage	73
Evidence of obstruction as shown by repeated vomiting morning gastric retention of more than 500 cc, or 50% residue of barium in six hours	50
Patients with previous hospital admission for medical therapy of ulcer	78
Patients with previous hospital admission for perforation of ulcer	26

Group A Patients with intractable pain, unrelieved by repeated medical treatment, many of whom had one or more hospital admissions for an ulcer "cure" The majority had had episodes of gastro-intestinal bleeding, and not a few were suffering from the effects of pyloric or duodenal obstruction

Group B Patients with actively bleeding ulcers This group was composed of those who entered the hospital during or within a week of severe gastro-intestinal hemorrhage, and in whom the hemoglobin was below 60 per cent (Sahli) Only one patient was operated upon during the acute phase of a massive hemorrhage, the remainder were explored when the bleeding had apparently ceased This group did not include patients who described several episodes of bleeding, but who entered the hospital in the interim, nor those who subsequently were readmitted for surgery after convalescence from a previous exsanguinating hemorrhage These cases, when operated upon, were placed in Group A

Group C This group comprised those patients in whom an acute perforated duodenal ulcer had previously been sutured, and in whom a recurrence of active ulcer disease or mechanical obstruction had developed

The relation of sex and age in these three groups is given in Table III

TABLE III  
ANALYSIS OF AGE AND SEX IN SUBGROUPS

	Sex		Ages					
	Male	Female	10-19	20-29	30-39	40-49	50-59	60 plus
A Duodenal ulcer 115 cases	94	21	0	12	27	42	34	0
B Bleeding duodenal ulcer 32 cases	31	1	0	6	7	13	3	3
C Previously perforated duodenal ulcer 26 cases	25	1	1	3	8	8	5	1
Total 173 cases	150	23	1	21	42	63	42	4

## PHYSICAL EXAMINATION AND LABORATORY DATA

A general physical examination was made by a member of the surgical staff, and an internist especially assigned to the ward surgical service for this purpose The physical findings were variable Evidences of recent weight loss and dehydration were found in those who had suffered the effects of intractable pain and pyloric obstruction A slight anemia was present in most patients Some patients in whom the bleeding had been severe were quite pale, showing definite clinical evidence of recent pronounced blood loss, however, it was rather interesting that in ten cases the hemoglobin was over 100 per cent The association of polycythemia and duodenal ulcer has frequently been mentioned

Chemical examination of the blood was routinely made for evidences of azotemia, hypoproteinemia and alkalosis. In two cases only, in which vomiting had been severe and protracted, were the clinical signs of alkalosis, as evidenced by tetany, readily discernible. However, the blood examinations revealed definite chemical evidences of alkalosis in seven other patients. This small number probably does not represent a true index of the frequency of this complication, for in this series adequate parenteral therapy was instituted frequently before the blood was drawn for chemical determinations. Varying degrees of azotemia and hypoproteinemia were present in many patients.

An increase above normal in the free and total acidity was uniformly observed in the Rehfuess test meals and in the examinations of the night-fasting gastric contents. Gastric analysis after the administration of insulin was done on a few patients in whom vagotomy was anticipated as a complementary procedure to subtotal gastrectomy.

Fluoroscopic and roentgenologic examinations were performed before or during hospital admission. The characteristic finding was a deformity of the duodenal bulb and occasionally an ulcer crater. Appreciable gastric retention of barium was found in 51 cases, but this roentgenologic finding was not always confirmed by the clinical evidences of retention. Gastroscopic examinations in patients suffering from duodenal ulcer were found to be of no direct value.

#### PREOPERATIVE PREPARATION

The majority of these ward patients who had suffered for many years from the devitalizing effect of chronic recurrent ulceration were in exceedingly poor general condition. Many showed the effects of severe physicochemical imbalances: the results of inadequate nutrition, intractable pain, persistent vomiting, or bleeding. As a group, these patients were obviously poor operative risks, and, therefore, required careful preoperative preparation.

All patients were given a period of complete bedrest. Whenever possible a high protein diet was prescribed, and essential vitamins were administered orally or parenterally. Pain was controlled with mild sedatives, aluminum hydroxide, atropine, frequent bland feedings and, occasionally, the milk or amphojel drip, as advocated by Winkelstein, Cornell and Hollander<sup>1,2</sup>. Anemic patients were given repeated transfusions of whole blood until the hemoglobin was raised to above 80 per cent. Every patient received a daily intravenous infusion of 1500 cc of saline and glucose. This was increased to about 4000 cc if vomiting had been a prominent symptom and a negative oral fluid balance existed because of pyloric obstruction. In these cases, the dilated atonic stomach with its stagnant contents was lavaged morning and evening with hot water through a large gastric tube. The importance of these lavages cannot be overemphasized. As a rule the inflammatory reaction about the duodenum or spasm of the pylorus subsided sufficiently so that gastrointestinal continuity was restored with the cessation of vomiting, a marked diminution in pain and a general clinical improvement of the patient.

Hypoproteinemia, which was not infrequent, usually responded to a high protein diet. If this was not feasible, plasma and blood transfusions, often supplemented by the intravenous use of amino-acids, elevated the lowered blood proteins to approximately normal levels. A preliminary jejunostomy for alimentation was performed in two patients suffering from pyloric obstruction, hypoproteinemia and alkalosis, who had failed to improve under conservative medical management. Their response to jejunal alimentation was immediate and striking, for within a short time gastroduodenal continuity was restored and the chemical imbalances were corrected. Subsequent subtotal gastrectomy was followed by uneventful recovery.

Twenty cases were treated preoperatively with therapeutic doses of desoxycorticosterone, but as no definite benefits were noted empirically, its use was discontinued. Sulfonamides were not used preoperatively.

#### ANESTHESIA

Inhalation anesthetics of various types were administered during the first three years. During the second three years, continuous spinal anesthesia was used, with ever increasing frequency. The total dosage injected was about 200 mg of procaine hydrochloride. Patients who were unduly apprehensive, or otherwise uncooperative, were given small doses of pentothal sodium intravenously. Continuous spinal anesthesia provided such excellent relaxation that adequate exposure was obtained with relatively few intra-abdominal packings and little retraction. Unfortunately, however, it did not diminish the incidence of pulmonary complications, which still contribute, in large part, to the morbidity and mortality of the operation.

#### OPERATIVE PROCEDURE

The incision regularly employed was midpigastrie, extending from the ensiform cartilage to the umbilicus. This was found to give adequate exposure in most cases. In a few especially obese patients, a right subcostal incision from the ensiform to the tip of the eleventh rib provided better access to the duodenum.

The operation of choice for duodenal ulcer in this clinic is still subtotal gastrectomy of the Billroth II-type. It is felt that this operation affords relief of symptoms in most cases, and is followed by the minimal incidence of recurrent gastrojejunal ulceration. But this operation is a complicated technical procedure which is often extremely difficult even in the hands of the more experienced. It is certainly not applicable to all patients suffering from chronic recurrent duodenal ulceration. It was contraindicated usually in those whose general poor condition did not respond to preoperative supportive treatment, in those who were extremely obese, in those who had passed the age of 65, and in those afflicted with severe cardiac disease or chronic nephritis. In these cases, a gastro-enterostomy was performed. In the six-year period, in which 223 patients were explored for chronic recurrent duodenal ulcer, a gastro-enterostomy was performed upon 48 patients, a pyloroplasty upon two patients, and a subtotal gastrectomy upon 173 patients.

TABLE IV  
CHOICE OF OPERATIONS

	Number	Per Cent
Total chronic duodenal ulcers operated upon	223	
Subtotal gastrectomy	173	77.6
Posterior gastroenterostomy	48	21.5
Pyloroplasty	2	0.9

Initially, the method of gastric resection, developed by Berg<sup>1</sup> and Lewisohn,<sup>4</sup> was followed. Gradually, however, definitive departures in technique were made. These will be only briefly described. After ligating the four cardinal arteries at appropriate points the stomach was transected proximal to the reentrant angle between a double layer of clips, laid down with the DePetz sewing machine. The distal gastric segment was turned to the right and the duodenum was carefully mobilized and divided by the open method, removing the ulcer whenever possible and practical. This frequently presented difficulties when the ulcer was extensive and the surrounding tissues were edematous, brawny and friable, or when the lesion penetrated deeply into the pancreas, or occupied the second portion of the duodenum.

TABLE V  
PATHOLOGY

Location	Number
Anterior wall (superior)	105
Posterior wall	48
Kissing type (anterior and posterior walls)	15
Second portion of duodenum	5

We do not feel that excision of the ulcer is an essential part of this procedure provided the pylorus is removed. (This was not undertaken in three cases in which a prepyloric "*auschaltung*" was performed.) In the present series of 173 cases, 102 resected specimens were found to contain the ulcer when examined by the pathologist. With the complete side-tracking of the acid gastric contents any ulcer in the isolated duodenum, bathed in its alkaline secretions will heal completely. Recurrence of an ulcer in the duodenal stump is practically unknown. Furthermore, Mage,<sup>5</sup> in a carefully conducted follow-up study of patients who had had a previous subtotal gastrectomy, concluded that recurrent gastrojejunal ulceration was no more frequent in those patients in whom duodenal ulcer was left *in situ* than in those in whom it was excised.

The great hazard of subtotal gastrectomy centers about the successful closure of the transected duodenum. The initial chronic Connell inversion suture was reinforced with interrupted linen Lembert sutures. An attempt was made to bring the stump of the divided pyloric artery over the superior angle of the sutured duodenum, and the stump of the divided gastro-epiploic artery over the inferior angle. The closed duodenum was then buried against the head of the pancreas with interrupted plain catgut sutures.

Drainage of the duodenal stump has been used with greater frequency during the past three years because of the possibility of a duodenal dehiscence.

It has become routine in almost all cases in which the security of the duodenal closure was questioned. A rubber dam, introduced through a right subcostal stab incision, was sutured with plain catgut to the duodenal stump. For a time, ten grams of sulfanilamide were deposited in this area, but this procedure has been abandoned.

Following resection, gastro-intestinal continuity was established at first by the usual retrocolic terminolateral gastrojejunostomy of the Hofmeister-type. During the past three years this isoperistaltic anastomosis has been made *anterior* to the colon utilizing a short proximal loop of jejunum, about six inches long. In an extensive and careful follow-up no differences have been noted in the functioning of the anterior anastomosis as compared with the posterior anastomosis. We have been impressed with the simplicity and advantages of the antecolic gastrojejunostomy. It has made the operation somewhat easier and has eliminated the incision in the transverse mesocolon which caused difficulty in six patients in whom the mesocolon was short. If subsequent gastrojejunal ulceration should develop at the site of this anterior anastomosis (which has not yet occurred in this series) secondary resection of the jejunum and stomach would certainly be less complicated. There is less possibility of the anastomotic ulcer penetrating into the colon and no possibility of injury to the middle colic artery in secondary operative procedures.

If, at the time of exploration, the stomach was markedly atonic and dilated, or if an appreciable retention has been present prior to operation, or if the duodenal closure was difficult and dehiscence of the suture line was a possibility, a complementary jejunostomy of the Kader-Stam type was performed for alimentation. This permitted feeding of a special pabulum containing all essential foods, vitamins, and electrolytes within 24 hours after operation, and resulted in the early curtailment of parenteral feeding. If a duodenal fistula developed, the drainage, if profuse, was immediately aspirated by continuous suction using the Stedman pump, thereby protecting the skin from the ravages of pancreatic digestion. The aspirated material containing intestinal, pancreatic, and biliary secretions was subsequently introduced through the jejunostomy tube. In some cases of gastric atony in which the drainage from the indwelling Levin tube was excessive and prolonged the instillation of the acid gastric secretion into the jejunostomy aided in the prevention of alkalosis. A complete discussion on the advan-

TABLE VI

	Stgr *	Stgr †	Jejunostomy			Drainage	
			Comp	Prel	Sup ‡	Yes	No
A Duodenal ulcer	27	88	24	1	0	66	49
B Bleeding duodenal ulcer	11	21	2	1	1	19	13
C Previously perforated duodenal ulcer	9	17	6	0	1	16	10
	47	126	32	2	2	101	72

\* Subtotal gastrectomy with retrocolic terminolateral gastrojejunostomy

† Subtotal gastrectomy with antecolic terminolateral gastrojejunostomy

‡ Complementary, preliminary, supplementary



tages of jejunostomy for alimentation has been described elsewhere<sup>6</sup> Table VI lists the type of gastro-enteric anastomosis, the institution of drainage, and the use of jejunostomy in each of the three groups

After the operation has been completed, the median epigastric incision was closed with heavy silk sutures passed through all the layers of the abdominal wall. This type of closure can be effected rapidly, and wound dehiscence, with evisceration, which was formerly frequent in midline incisions, has been practically eliminated. This type of closure, however, is accompanied by an appreciable number of postoperative herniae.

#### POSTOPERATIVE COURSE AND COMPLICATIONS

Postoperatively, a Levin tube was left indwelling and an intravenous infusion of saline and glucose, which was given throughout the operation, was continued. If there was moderate blood loss or any degree of shock, the patient was transfused. Oral fluids in small amounts were allowed within 24 hours after operation. Sulfonamides were not administered routinely.

The Levin tube was usually removed about the third day, unless signs of gastric retention were evident. Adequate sedation was administered. The patients were encouraged to move about. The through-and-through sutures were removed in ten days, at which time patients were permitted out of bed.

There were no instances of immediate postoperative hemorrhage. Two patients experienced a small hematemesis about the tenth day, but this was easily controlled with conservative measures.

Difficulties in gastric emptying were not unusual, but in the majority of patients these were transitory and without significance. A severe gastric atony occurred in three cases in which a complementary jejunostomy had not been undertaken. In one patient, an entero-anastomosis was performed 14 days after the primary operation, without relief of the gastric ileus. Subsequent postmortem examination failed to disclose any mechanical reason for the vomiting and alkalosis. This case impressed us with the seriousness of this complication, and was the reason for the subsequent frequent institution of complementary and supplementary jejunostomy for alimentation in indicated cases. In two other patients suffering from gastric atony, a supplementary jejunostomy, because of an alkalosis, was performed within a week of the primary operation, and recovery was uneventful.

Physical signs of a localized peritonitis were occasionally present in the right upper quadrant of the abdomen, and in some, a mass eventually became palpable. This was due probably to an inflammatory exudate about the duodenum and pancreatic head. In the majority of cases this subsided spontaneously, but in two patients an incision and drainage of an abscess became necessary. However, if the entire abdomen was tender and rigid, a general peritonitis arising from duodenal dehiscence was suspected. A duodenal leak was usually a fatal complication if the duodenal stump had not been drained. It almost inevitably resulted in a generalized peritonitis, a subhepatic abscess, or a right or left subphrenic abscess. The small subhepatic collections were usually absorbed spontaneously, but once a

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diagnosis of a subphrenic purulent accumulation was substantiated roentgenologically and by exploratory puncture, surgical drainage was performed. Subphrenic abscess was a serious complication and death occurred in three of five patients who were drained.

The danger from a duodenal leakage was materially lessened by the use of drainage which as has been previously indicated, is being instituted with increased frequency. The presence of a rubber dam in the vicinity of the duodenal suture line apparently did little harm. There was evidence of duodenal damage along the dam in approximately 13 cases, but in only two of these did a general peritonitis develop. Most duodenal leaks made their external appearance on the third or fourth day, others were not apparent until the ninth or tenth day. This varied in degree from a slight biliary staining of the dressing to a profuse intestinal discharge which was only controlled by continuous suction drainage with a Stedman pump. There were three cases in which, after the duodenal secretion had ceased, a purulent drainage persisted for three months. This was undoubtedly due to a residual infection about the linen Lembert sutures. All these sinuses however, subsequently healed. There was no instance in which either a spreading peritonitis or localized intra-abdominal abscess could be ascribed to a dehiscence of any part of the Hofmeister type of terminolateral gastrojejunostomy.

Five patients became jaundiced postoperatively. The icterus in four cases was apparently the result of sulfonamide therapy. The fifth case was never properly explained, but the jaundice eventually disappeared, and the patient ultimately recovered.

Wound infections were rather infrequent rarely contributed to the morbidity, and never to the mortality of the operation. In three cases in which the wounds were not sutured with the usual "through-and-through" closure a disruption occurred, but no evisceration occurred in any cases in which the routine closure was used.

The incidence of pulmonary complications, which were mainly pneumonic and atelectatic in nature, was high. In a few seriously ill patients, a rapidly performed bronchoscopy with suction removal of the mucous plug was responsible for a prompt and dramatic recovery. While the judicious use of sulfonamides did much to render pulmonary complications less severe, there were five deaths attributable to pneumonia. One patient died of a pulmonary embolus, and one of a cerebral thrombosis.

An analysis of the mortality in the three previously described groups is outlined in Tables VII A and B. A résumé of the causes of 12 deaths determined in nine instances by postmortem examination, is detailed in Tables VIII A and VIII B. A comparison of the two series is given in Table IX.

## DISCUSSION

A study of Tables VII, VIII, and IX shows that there was a significant difference in mortality between Series A (July 1, 1937 to June 30, 1940) and

TABLE VII A  
ANALYSIS OF DEATHS IN SUBGROUPS

<i>Series A</i>				Mortality Rate
	No of Cases	No of Deaths	Cause of Death	
Duodenal ulcer	48	3	(1) Cerebral thrombosis (2) Generalized peritonitis (3) Alkalosis	6 25%
Bleeding duodenal ulcer	16	3	(1) Duodenal dehiscence Generalized peritonitis (2) Hemorrhagic bronchopneumonia (3) Subphrenic and subhepatic abscesses	18 75%
Previously perforated duodenal ulcer	15	2	(1) Massive atelectasis (2) Pneumonia after drainage of subphrenic abscess	13 33%
Total	79	8		10 13%

TABLE VII B  
ANALYSIS OF DEATHS IN SUBGROUPS

<i>Series B</i>				Mortality Rate
	No of Cases	No of Deaths	Cause of Death	
Duodenal ulcer	67	3	(1) Hepatitis and pneumonia (2) Pulmonary embolism (3) Diffuse bronchopneumonia	4 48%
Bleeding duodenal ulcer	16	1	(1) Duodenal dehiscence Subhepatic abscess	6 25%
Previously perforated duodenal ulcer	11	0		0
Total	94	4		4 26%

Series B (July 1, 1940 to June 30, 1943) In Series A death was the eventual result of a duodenal leak in four cases, while in Series B this complication occurred in only one instance. The improvement was undoubtedly due in part to the increased skill of the operators in effectively mobilizing the duodenum so that its closure was more secure. Then, too, the wider use of drainage probably acted as a safety vent in those cases in which a duodenal dehiscence developed. If these cases had not been drained, a fatal generalized peritonitis might have resulted. This contention is further illustrated in the analysis of the causes of death in those patients who had had a previously perforated duodenal ulcer (Group 3, Table VII). In these secondary cases, the duodenum was fibrosed, distorted, and surrounded by firm dense adhesions. Mobilization was difficult, and closure was even more difficult. The fact that no deaths occurred in this group in which drainage was liberally used might be a commendation for this innovation.

The use of jejunostomy for alimentation both as a complementary and supplementary procedure, undoubtedly prevented and corrected many of the physical and chemical imbalances incident to postoperative gastric atony and alkalosis. In the past, these serious and untoward complications have often contributed materially to the morbidity and mortality of gastric and duodenal surgery.

Spinal anesthesia provided better relaxation, and this, combined with the antecolic type of gastrojejunostomy, simplified the technical aspects of the entire operative procedure. It is to be noted in Table IX that the lowered

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TABLE VIII A  
DECEASED CASES—SERIES A

No and Initials	Age and Sex	Diagnosis	Anesthesia and Operation	Cause of Death (Postmortem Findings)
455130 I M	56 Female	Duodenal ulcer Arterio-sclerotic cardiovascular dis	Gas—oxygen—ether Subtotal gastrectomy, with antecolic anastomosis Drained	Cerebral thrombosis with hemiplegia (8 days P O )
437484 M S	51 Male	Duodenal ulcer	Avertin—ethylene Subtotal gastrectomy, with retrocolic anastomosis	No postmortem obtained Generalized peritonitis (8 days P O ) No postmortem obtained
432792 S S	41 Female	Duodenal ulcer Hyper-tensive cardiovascular disease	Avertin—ethylene Subtotal gastrectomy, with anterior anastomosis Secondary entero-enterostomy 14th P O day	No anatomic reason for death Clinical impression alkalosis (32 days P O )
424871 J K	55 Male	Bleeding duodenal ulcer	Avertin—ethylene Subtotal gastrectomy, with retrocolic anastomosis (Auschaltung, prepyloric)	Dehiscence of duodenal stump Generalized peritonitis (7 days P O )
419123 K H	38 Male	Duodenal ulcer (previously perforated)	Avertin—ether Subtotal gastrectomy with antecolic anastomosis Vagotomy	Massive atelectasis Pneumonitis (2 days P O )
433621 A L	46 Male	Bleeding duodenal ulcer	Avertin—ethylene Subtotal gastrectomy with antecolic anastomosis	No postmortem obtained Severe hemorrhagic bronchopneumonia (16 days P O )
438885 D E	48 Male	Bleeding duodenal ulcer	Avertin — ethylene Subtotal gastrectomy, with retrocolic anastomosis Drained Supplement-ary jejunostomy for alimentionation	Subhepatic and subphrenic abscesses Fibrinous peritonitis (42 days P O )
457697 B S	39 Male	Duodenal ulcer (previously perforated)	Ethylene Subtotal gastrectomy with antecolic anastomosis Drained Secondary drainage of left subphrenic abscess	Pneumonia (died 6 days after drainage of subphrenic abscess and 24 days after gastrectomy)

TABLE VIII B  
DECEASED CASES—SFRIES B

No and Initials	Age and Sex	Diagnosis	Anesthesia and Operation	Cause of Death (Postmortem Findings)
485833 L K	58 Male	Duodenal ulcer	Continuous spinal Subtotal gastrectomy, with antecolic anastomosis Drained Intrapertitoneal sulfanilamide	Hepatitis and pneumonia (17 days P O )
491002 I D	54 Male	Duodenal ulcer Essen-tial hypertension	Continuous spinal Subtotal gastrectomy, with antecolic anastomosis Intrapertitoneal sulfanilamide Drained	Pulmonary embolism Bronchopneumonia Pul-monary edema (1 day P O )
501861 J M	58 Male	Duodenal ulcer	Continuous spinal Subtotal gastrectomy, with antecolic anastomosis Drained	Diffuse bronchopneumonia (7 days P O )
460231 J B	42 Male	Bleeding duodenal ulcer	Cyclopropane Subtotal gastrec-tomy with antecolic anastomosis Drained	Dehiscence of duodenal stump Generalized perito-nitis (healing) Subhepatic abscess Died 34 days P O

TABLE IX  
COMPARISON OF THE STATISTICS IN SFRIES A AND B

	Series A July 1 1937 to June 30, 1940	Series B July 1 1940 to June 30, 1943
No of cases	79	94
Mortality	8	4
Mortality percentage	10 13	4 26
Drainage of duodenal stump	29	72
Antecolic type of gastrojejunostomy	35	91
Retrocolic type of gastrojejunostomy	44	3
Jejunostomy	4	32
Spinal anesthesia	16	84
General anesthesia	63	10

mortality in the second group may be ascribed in part to spinal anesthesia, the wider use of drainage of the duodenum, the antecolic type of anastomosis, and the frequent employment of jejunostomy for alimentation

When the mortalities of the three groups are considered individually (Table VII A and B), it is found to be highest in the bleeding ulcers. In Series A the mortality was 18.75 per cent. Sixteen patients were explored as soon as blood and plasma transfusions had elevated the hemoglobin, increased the number of red blood cells and raised the blood pressure. There were three deaths. Apparently the impoverished tissues of the body were slow to recover from the recent effects of anoxemia so that healing was impaired, a dehiscence of the stump was more likely and pulmonary complications were more frequent.

In Series B, an equal number of patients were operated upon with one death, a mortality rate of 6.25 per cent. These patients were not explored until three to four weeks had elapsed following hemorrhage, and they had partially recuperated from the general systemic effects of their blood loss. In the future, all patients suffering from bleeding duodenal ulcer will be discharged from the hospital if possible, for convalescent care and radical surgery will be performed only when their general condition has approximated normal. This conservative attitude in the treatment of bleeding ulcer may be criticized by those who advocate early operation, frequently within 48 hours in those patients over 45 years of age. However, we agree with the conclusions of Crohn and Lerner<sup>7</sup> that, by and large, better results will be obtained in acute hemorrhage if these patients are treated medically during the acute phase. Radical surgery may then be subsequently performed when bleeding has ceased and the patients have fully recovered from the general effects of exsanguinating hemorrhage.

The problem of pneumonia is still apparently unsolved. The use of sulfonamide drugs and judicious application of bronchoscopy have undoubtedly lowered mortality from this complication, but pneumonia still seems to be an unavoidable and, only too often, fatal complication of upper abdominal surgery.

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# HEMOSTASIS WITH ABSORBABLE GAUZE\*

(OXIDIZED CELLULOSE)

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A PRELIMINARY REPORT of our observations of tissue reactions to oxidized cellulose† appeared in the ANNALS OF SURGERY in July, 1943. This represented experimental work undertaken in 1941, and the results agreed with those of Ingraham and Bailey, reported in 1944, who checked the tissue reactions and compared them to those obtained with fibrin foam.

In the same issue of the ANNALS Dr Tracy J Putnam reported his clinical use of the material as a carrier for thrombin to secure hemostasis in neurosurgery. At that time further investigation was planned to determine the degree of oxidation, *i e*, percentage of carboxyl groups, yielding the most satisfactory product for clinical use and a reliable method for sterilization of the material, which does not withstand the process in the autoclave. At the moment of writing, the gauze supplied for clinical investigation contains approximately 13.5–15.8 per cent COOH, and is submitted, doubly packaged, in glassine envelopes after formaldehyde sterilization, which has been checked aerobically and anaerobically, and which does not leave sufficient trace of formaldehyde to render the material irritating on this account. Cotton pledgets, similarly packaged, contain 10–12.5 per cent COOH.

When the relatively nonirritating nature of the cellulose had been established, and it had been shown that, in small amounts at least, it was absorbed in varying lengths of time from different tissues, there was an immediate demand for the release of the gauze for clinical use in cases of hemorrhage where hemostasis could not be secured by ligature or other methods, and where ordinary gauze packing, with all the well known difficulties of subsequent removal, had to be used as a last resort. There were many suggestions offered as to use of the material in traumatic surgery, naturally, with military necessity in mind, where packing of wounds with ordinary gauze, used for

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† The gauze and cotton were supplied by Eastman Kodak Research Laboratories, Rochester, N Y (U S Pat No 2,232,990), through Parke, Davis & Company, Detroit, Michigan.

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hemostasis, had so often resulted in sealing-up of deep contamination, with resulting serious wound infection

Accordingly, a series of experiments were undertaken to reproduce, as nearly as possible, lacerated bleeding wounds such as those which in clinical practice might necessitate gauze packing. No adjuvant to promote clotting was used, and no immediate effect was expected other than cessation of bleeding inherently due to the presence of the packing. Standard procedures were worked out, after trial and error, in which the type and extent of bleeding



FIG 1—Photomicrograph showing oxidized gauze in experimental wound of kidney 48 hours after packing. The gauze is closely applied to the wound surfaces (Low power)

could be anticipated, and in which the effectiveness of packing could be estimated. This estimation was, needless to say, based not on any measuring or timing, but on clinical impression. With repeated observations, however, certain unexpected findings were established.

- 1 The oxidized gauze was easier to pack into a bleeding wound than ordinary gauze. It seemed more pliable, and, when wet with blood, slightly sticky.

- 2 The oxidized gauze, used dry, was observed to swell when saturated with blood, and this was a second factor which facilitated packing—the gauze easily filling all the irregular crevices in the wound (Fig 1).

- 3 The combination of blood and oxidized gauze resulted almost immediately in a dark-brown or black mass and as soon as this discoloration

occurred bleeding usually ceased (The affinity of the oxidized material for hemoglobin and its effect on this may be seen by immersing a strip of gauze in a test tube of dilute laked blood. Almost immediately the hemoglobin is drawn into the gauze turning brown, and leaving the solution colorless (Fig 2)

4 The hemostatic effect appears to depend *not on clotting* within the meshes of the gauze but on the *swelling* of the material and its *sticky character* when blood-soaked, so that the packing itself *takes the place of clot*. We have not studied any possible *direct* effect on the clotting process.

5 Neutralization of the material with calcium acetate resulted in the loss of the above properties rendering it less effective as an hemostatic.

6 As early as 24 hours after packing the oxidized gauze was so friable that it broke when an attempt was made to withdraw it in contrast to ordinary gauze which could be withdrawn but which in clean wounds especially, was usually stuck so that force was necessary for withdrawal. With ordinary gauze removal was apt to be followed by bleeding, sometimes requiring secondary packing. With oxidized gauze by 48 hours in an open wound, the gelatinous mass of brown material which represented the blood-soaked packing could be gently scraped away from the wound surface without renewal of bleeding (Fig 3)

7 Oxidized gauze even when not absorbed early was not invaded by reparative tissue. The foreign body therefore was not incorporated in scar to any extent, and scarring was minimal.

8 In serous cavities where a relatively large single mass of material is surrounded by serous membrane, cysts are sometimes formed. These apparently can eventually resorb and have been in general small not proportional to the amount of gauze used. Such cysts have not been observed in solid viscera or the supporting tissues—connective tissue, muscle, bone (The work on serous cavities is not complete as regards the study of adhesions but is reported here to illustrate the tissue reaction to large amounts of gauze)

The observations summarized above are based on experiments in which the wounds were made with the animals under general anesthesia and with aseptic precautions.



FIG. 2.—Photograph showing oxidized gauze in dilute laked blood—right, control without gauze—left. The control was bright red. The gauze was brown and the supernatant fluid almost colorless.



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GAUZE PACKING—48 HOURS

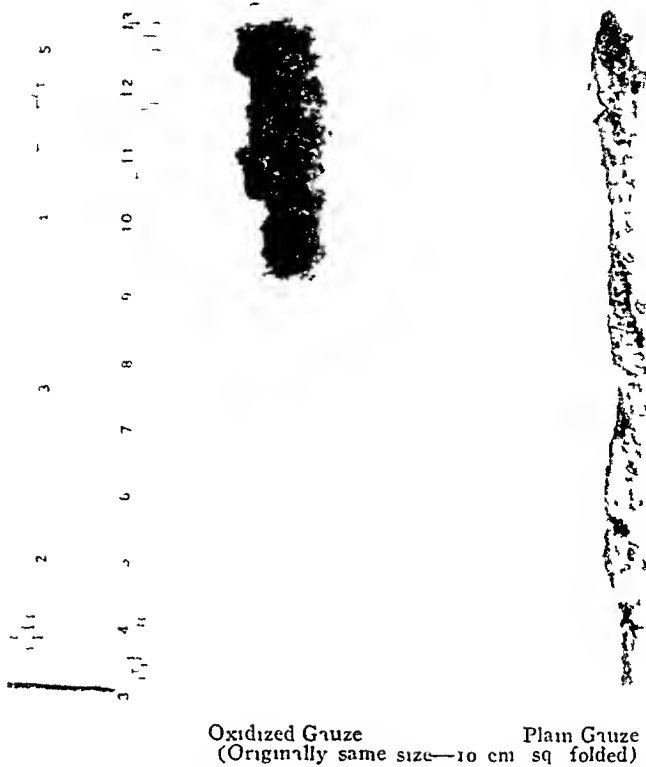


FIG 3—Gauze packing withdrawn from experimental wounds of kidney after 48 hours. The oxidized gauze was black and friable. The plain gauze was stained with bright red blood.

22053  
WOUNDS OF LEFT KIDNEY—5 DAYS  
Upper Pole Gauze—Oxidized (7 Hours)      Lower Pole Gauze—Plain



HILUS

FIG 4—Autopsy specimen, five days after operation. See Table I, S. P. 22053. At four days an attempt had been made to remove both packings. The oxidized gauze (Eustman OR 1352 B, 7 hour oxidation sample, 13.5-13.8 per cent COOH) was too friable to be withdrawn completely. Through an error, only one of the two strips of plain gauze was withdrawn. No bleeding occurred. Twenty-four hours later the animal was sacrificed. The kidney has been sectioned through the two wounds showing their size and the gauze packing. On the convex surface of the upper pole there is properitoneal fat.

# HEMOSTASIS WITH ABSORBABLE GAUZE

## EXPERIMENTS WITH HEMOSTASIS WITH CLEAN WOUNDS OPEN (Kidney, Spleen, and Liver)

The kidneys were delivered extraperitoneally, through an oblique muscle-splitting incision in the flank. Wounds were made, as nearly as possible similar in the upper and lower poles, by an incision about 1.5 cm in the capsule, which was deepened by blunt dissection so that the medulla was reached but the pelvis was avoided, and spitting bleeding was obtained. The wound in the upper pole was then packed with oxidized gauze, various

TABLE I  
HEMOSTASIS IN OPEN WOUNDS OF VISCERA  
(Oxidized Gauze—Eastman OR-1352-B)

S P No Animal	Organ	Time Postoper	Result				
			Oxidized Gauze			Control Gauze	
22020 Dog	Kidney	24 hours	Gelatinous bleeding	Easily expressed	No	Stuck	Bleeding after removal Ceased spontaneously
22025 Dog	Kidney	48 hours	Gelatinous by thin brown fluid	Scooped out	Followed	Stuck	Bleeding after removal Packed with oxidized gauze
22059 Dog	Kidney	48 hours	Disintegrated bleeding	No free fluid	No	Stuck	Bleeding after removal Packed with oxidized gauze
22058 Dog	Kidney	48 hours	Disintegrated dressing, gush of thin brown fluid	Came away with		Stuck	Bleeding after removal Stopped spontaneously
22021 Dog	Kidney	52 hours	Gelatinous wound No fluid	Loose in mouth of		Did not control bleeding at oper- ation	Oxidized gauze used
22052 Dog	Kidney	4 days	Gone from mouth of wound	Dressing dry		Stuck	Bleeding after removal Repacked with oxidized gauze
22053 Dog	Kidney	4 days	Disintegrated gelatinous fluid	Pressure yielded		Stuck	Only one strip removed No bleeding Second strip found at autopsy 5th day
22025 Dog	Spleen	48 hours	Negligible remnant wound) No bleeding	(Infected)		Stuck	Bleeding after removal requiring repacking
22058 Dog	Spleen	48 hours	Gelatinous bleeding	(Infected wound)	No	Stuck	Bleeding after removal Animal voided blood Sacrificed
22059 Dog	Spleen	48 hours	Negligible remnant wound) No bleeding	(Infected)		Stuck	Moderate bleeding after removal Animal sacrificed
22078 Dog	Spleen	48 hours	Loose in wound removal	No bleeding after		Stuck	Slight bleeding Animal sacrificed
22079 Cat	Spleen	48 hours	Gelatinous	No bleeding		Stuck	Slight bleeding Animal sacrificed
22061 Dog	Liver	24 hours	Packing in place bleeding	Crumbles	No	Stuck	Slight ooze Animal sacrificed

samples, and the wound in the lower pole by plain gauze (Fig 4). In one instance, No. 22021, the kidney was badly traumatized at the lower pole and bleeding could not be controlled by packing with ordinary gauze. Oxidized gauze was, therefore, used and hemostasis secured.

In the case of the spleen exteriorization was three times accomplished through a left lumbar incision at a secondary procedure after nephrectomy of a previously injured kidney. These cases were all infected. Twice a left rectus approach was used. Only one exteriorization of the liver was performed in a survival animal, and this was accomplished through a transverse upper abdominal incision and the liver secured in the wound by tamponade. Repeated observations, however, in anesthetized animals, were made, just prior to death from overdose of anesthesia, of immediate control of

bleeding in all these viscera with various samples of material The results are noted in Table I

EXPERIMENTS IN HEMOSTASIS WITH CLEAN WOUNDS CLOSED  
(*Kidney, Spleen, Liver, Thyroid and Bone*)

Further investigation of the late effects on the tissue of trauma and packing were then undertaken. The wounds were closed.

*Kidney*—The technic used for the kidney differed from that employed for open wounds only in that the approach was transperitoneal, through a left rectus incision, and the packing was not allowed to protrude from the viscus, but was cut flush with the surface and a single marking black silk suture was tied loosely over it.

*Spleen*—The spleen was also delivered through a left rectus incision. Wounds were then made by excising a rectangular piece of tissue approximately  $2 \times 1 \times 0.3$  cm from the upper surface. Bleeding was always brisk. It was controlled by placing a  $10 \times 10$  cm square of oxidized gauze, folded over the defect, and a similar folded sponge of the same material on the opposite surface, securing the two by through-and-through sutures of black silk. This "sandwich" type of packing controlled bleeding quickly. The material used was Eastman OR-1352-B, 7-hour oxidation, and Parke, Davis No. 098630, 5-6 hour oxidation, 13.5-15.8 per cent COOH. The results are noted in Tables II and III.

*Liver*—Because of the difficulty of approach and the anaerobic infections which occasionally occur in dogs following liver injuries, this organ was used only five times. Hemostasis was immediately satisfactory in all five cases whether the gauze was packed into deep wounds in the parenchyma, or used as "sandwich" packing to staunch bleeding from a shallow surface defect. Four of the animals have come to autopsy, at 31, 35, 36, and 42 days, respectively. There was one abscess in which an *hemolytic Staphylococcus aureus* and *C. welchii* were found on culture. This was well walled-off, and there was no infection of the spleen wound in the same animal. In all four the gauze was entirely absorbed.

*Thyroid*—Four cases have been studied. The right lobe of the thyroid was split along the convex border, the wound was enlarged by blunt dissection and oxidized cotton, Parke, Davis No. 098631, packed into the cavity from which bleeding was always brisk. At two weeks the material had not been absorbed (Fig. 10). At four, five, and six weeks the material was entirely absorbed, and the injury was represented by a zone of characteristic phagocytes.

*Bone*—Experiments on bone are not complete, due to the length of time required for histologic preparation. Defects have been made repeatedly in the radius, and bleeding was quickly and easily controlled by packing, which was made tight. In such rigid-walled cavities the material could be made to fill the crevices almost like gutta serena. Callus has been shown in some cases roentgenologically, but complete data are not yet at hand.

# HEMOSTASIS WITH ABSORBABLE GAUZE

TABLE II

KIDNEY PACKINGS—TWO EACH CASE—UPPER AND LOWER POLES

S P No Animal	Time Days	Result
22125 Cat	21	Largely absorbed
22155 Dog	23	Micros Remnants Many phagocytes
22118 Rabbit	28	Partly absorbed
22181 Dog	28	Micros Many phagocytes
22248 Dog	29	Grossly absorbed
22257 Dog	29	Micros Remnants Many phagocytes
22220 Dog	30	Partly absorbed
22146 Dog	31	Micros Some polymorphonuclears Many phagocytes
22191 Dog	33	Largely absorbed
22154 Dog	35	Micros Remnants Many phagocytes
22256 Dog	35	Almost all absorbed
22157 Dog	36	Micros Remnants Many phagocytes
22214 Dog	37	Largely absorbed
		Micros Remnants Many phagocytes
		Partly absorbed
		Micros Considerable amount Many phagocytes
		Almost entirely absorbed
		Micros Phagocytes
		Almost entirely absorbed
		Micros Occasional fiber Phagocytes
		Lower pole—absorbed entirely Micros Phagocytes
		Upper pole—absorbed very little Micros Phagocytes Giant cells
		Absorbed
		Micros Rare fiber in one pole Phagocytes
		Absorbed
		Micros Rare fiber in one pole Phagocytes

TABLE III

OXIDIZED GAUZE SANDWICH PACKING OF WOUND OF SPLEEN

S P No Animal	Time Days	Result
22125 Cat	21	Omental adhesions Gauze gelatinous
22311 Dog	22	Micros Phagocytes Giant cells Cicatrix
22312 Dog	22	Omental adhesions Some gross gauze present
		Micros Phagocytes Giant cells Polys
		V B This animal had a large amount of gauze also packed in the pelvis
22155 Dog	23	Omental adhesions Some gross gauze present
22181 Dog	28	Micros Phagocytes Giant cells Polys
22248 Dog	29	Omental adhesions A little gauze in wound
22257 Dog	29	Micros Some gauze both sides Phagocytes Few giant cells
22220 Dog	30	Omental adhesions No gross gauze
22146 Dog	31	Micros Gauze remnants Phagocytes Giant cells
		Omental adhesions No gross gauze
		Micros Few fibers both sides Phagocytes Many giant cells
		Omental adhesions No gross gauze
		Micros No gauze Few phagocytes Slight cicatrix
		Omental adhesions No gross gauze
		Micros Occasional gauze fiber Phagocytes
		Omental adhesions Bulk of gauze gone Scarring
		Micros Phagocytes and polymorphonuclear leukocytes (Liver abscess in this case)
22191 Dog	33	Omental adhesions No gross gauze
22154 Dog	35	Micros Remnants Phagocytes Moderate cicatrix
22256 Dog	35	Omental adhesions No gross gauze
22157 Dog	36	Micros Few fragments Phagocytes Marked cicatrix
22214 Dog	37	Omental adhesions upper and under surface No gross gauze
22356 Dog	40	Micros Remnants Phagocytes Giant cells
		Omental adhesions very delicate No gross gauze
		Micros Gauze fragments only upper surface Phagocytes
		Omental adhesions No gross gauze
		Micros No gauze Few phagocytes Slight cicatrix
		Omental adhesions No gross gauze
		Micros Tiny remnant Phagocytes

## EXPERIMENTS WITH GAUZE SPONGES WRAPPED IN OMENTUM

A sponge was made of a 10 x 10 cm square of oxidized gauze, and this was placed on the surface of the omentum. In most instances the sponge was dry. In a few cases it was first wet with the animal's blood. The omentum was then folded over it and tacked in place with two marking silk sutures. The results are noted in Table IV.

It will be seen from study of these tables that the time of absorption is variable. There are several possible factors in this connection which may all operate together but which may be discussed separately.

1 Amount of Material. Since disappearance of the material depends, at least in part, on solution, large amounts of gauze packed into small spaces might not readily be penetrated by tissue fluids, and absorption would be delayed. Penetration by phagocytes would also be slower the greater the bulk of the foreign body.

2 Degree of Injury. This is difficult to evaluate, but obviously the integrity of the circulation to the part would influence rapidity of absorption.

3 Amount of Blood Present. This would at least add to the bulk of material to be absorbed.

4 Nature of the Tissue. This is illustrated by the fact that in the kidney considerable delay was repeatedly found, whereas, in the omentum, for instance, absorption was, in general, more rapid. This may possibly be related to the lower  $p_H$  of the tissue fluids in the kidneys of laboratory animals (dogs and cats). On one determination upon homogenized kidney tissue of a dog the  $p_H$  was 6.63.

5 Lack of Uniform Degree of Oxidation. Occasional fibers of gauze remaining when the bulk is absorbed may, perhaps, contain a lower percentage of carboxyl groups.

These variables are all reflected in the gross and microscopic findings in the tissues which have been in contact with the material. In our earlier report in the ANNALS we submitted photomicrographs of the reaction of various tissues at varying intervals after operation. The amounts used were small, and a deliberate attempt was made to avoid all unnecessary injury and bleeding. In the present series, except in the omental implants, the tissues have been deliberately traumatized, and the gauze used for hemostasis. As was expected from our earlier experience there has been no acute inflammatory reaction to the material itself. There have been, however, phagocytic reactions, of varying degree. Where no great amount of hemosiderin is present, the phagocytes show large basophilic droplets in the cytoplasm. Almost no granulation tissue is present around the foreign body, and there are only rare infiltrating cells other than phagocytes. A characteristic zone is found, of typical large phagocytes showing intense basophilism, almost diagnostic for the material. Less detailed studies have been made with other materials, and while phagocytes are found in some instances, none has had this particular appearance. These variations and the histologic findings are illustrated in photomicrographs (Figs 5-10).

# HEMOSTASIS WITH ABSORBABLE GAUZE

TABLE IV  
OXIDIZED GAUZE SPONGE IN OMENTUM  
(Square 10 x 10 cm Folded)  
(Eastman OR-1352-B and Parke, Davis 098630)

S P No	Time	Surrounding Omentum	Character of Maternal	Microscopic Findings
21591 Cat	6 hours	Not inflamed	Easily cut with knife	Rare polys
21630 Cat	22 hours	Not adherent		No fibrin
21576 Cat	24 hours	Not adherent	Slightly gelatinous	No polys Slight edema
21579 Cat	30 hours	Slightly injected	Slightly gelatinous	No fibrin
21568 Cat	3 days	Not inflamed	Culture sterile	Scattered polys
21572 Cat	3 days	Not adherent	Light tan soft, fibrillar	No fibrin
21858 Dog	3 days	Thickened cystic cavity	Culture sterile	No reaction
21590 Cat	4 days	Thickened, cystic cavity	Mostly clear fluid	Polys
21600 Cat	5 days	Fibrinopurulent peritonitis (Previous appendectomy)	brown jelly Culture sterile	Fibroblasts
21886 Dog	7 days	Thickened, cystic cavity	Cloudy fluid	Fibrin Polys
21887 Dog	10 days	Thick-walled, cystic cavity	Culture sterile	Fibroblasts
21899 Dog	14 days	Thick-walled cyst Little inflammation	Light tan gelatinous fibrillar	Pus
21905 Dog	18 days	Thickened, cystic cavity	Clear fluid Culture sterile	Fibrin Polys
22125 Cat	21 days	Thick-walled, cystic cavity	Cloudy fluid Culture sterile	Fibroblasts
22155 Dog	23 days	Transparent cyst 2 cm	Clear fluid slightly blood-tinged Few fibers	Fibrin Polys Fibroblasts
22056 Cat	28 days	Dark red soft mass 1 2 cm	Thick white fluid Culture coagulase-pos Staphylococcus	Lining of phagocytes No polys Fibroblasts
22057 Dog	28 days	Thickening 4 mm	Brown cloudy fluid Culture Esch coli	Polys Phagocytes No fibroblasts
22181 Dog	28 days	Thickening 3 mm	Thick, white fluid Not cultured	Few polys Phagocytes Little fibroplasia
22248 N B	29 days	Transparent cyst 2 5 cm	Clear fluid	Rare polys Lining of phagocytes
22257 N B	29 days	Red-brown zone of thickening 1 cm	Soft solid on section	Few fibers phagocytes No polys
22220 Dog	30 days	This sponge had been soaked in blood	Entirely absorbed	Fragments of gauze Phagocytes
22146 Dog	31 days	Slight thickening, 0 8 cm	Entirely absorbed	Characteristic phagocytes
22191 Dog	33 days	Tiny zone of thickening marked by suture	Thin brown fluid and jelly	Characteristic phagocytes
22065 Dog	35 days	Slight omental thickening marked by suture	Center friable	Lining composed of phagocytes
22066 Cat	35 days	Thickening 0 5 mm marked by suture	Entirely absorbed	Considerable gauze Phagocytes
22154 Dog	35 days	Marking sutures found	Entirely absorbed	No gauze Characteristic phagocytes
22256 Dog	35 days	Marking sutures found	Entirely absorbed	No gauze Few phagocytes
22157 Dog	36 days	Light brown zone of thickening 1 cm	Entirely absorbed	No gauze Characteristic phagocytes
22214 Dog	37 days	Smooth-walled cavity	Entirely absorbed	No gauze Characteristic phagocytes
22356 Dog	40 days	Brown thickened zone 3 x 1 cm	Entirely absorbed	No polys
		Transparent cyst 2 5 cm	Brown mass 5 x 5 x 7 mm	Phagocytes No polys
		Brown thickening	Clear fluid	No gauze Thick zone of phagocytes
			Entirely absorbed	Fragments of gauze in fluid with some blood
				No gauze Phagocytes
				Few fibers fluid Characteristic phagocytes Scar

## CLINICAL INVESTIGATION

Clinical trial of the material was delayed until the formaldehyde sterilized material which was available had been checked for sterility and tested for irritating qualities in the tissues. It has been used for hemostasis in 17 cases. In four of these packing of some sort was imperative and, in two of the

TABLE V  
HEMOSTASIS IN CLINICAL CASES WITH SOLUBLE GAUZE AND COTTON

Case	Hist No	Date	Surgeon	Source of Bleeding	Closure	Result
1	633513	4/13/44	Stooley	Internal carotid	Closed	Sinus lower angle 6th day Closed 30 days No infection
2	741353	4/18/44	Whipple	Gallbladder bed	Drained	Tube out 9th day Healed 14th day
3	741879	4/22/44	Humphreys	Liver surface, through diaphragm	Intercostal drainage 48 hours	Healed 7th day
4	627664	5/1/44	St John	Incisional biopsy liver	Closed	Healed <i>per primam</i>
5	639170	5/4/44	Humphreys	Intercostal vein Sympathectomy	Closed	Hematoma followed by pleurisy with effusion
6	706699	5/6/44	Scudder	Metatarsal Amputation toe	Open Infected	Hemostasis satisfactory Removed 3rd day No bleeding
7	742421	5/11/44	Humphreys	Cervical lymph node Biopsy Ca	Closed	Hemostasis satisfactory Healed <i>per primam</i>
8	744514	5/12/44	Humphreys	Sternum Biopsy Leukemia	Closed	Hemostasis satisfactory Healed <i>per primam</i>
9	738341	5/13/44	Harvey	1 Plantar abscess Drainage	Open Infected	Hemostasis satisfactory Removed 24 hours No bleeding
		6/4/44	Harvey	2 Plantar abscess Revision of drainage	Open Infected	Hemostasis satisfactory Removed 3 days No bleeding
10	733473	5/13/44	Auchincloss	Gallbladder bed	Drained	Hemostasis satisfactory Slight bleeding 9th day Cause? Biliary fistula 2nd to 17th day Healed <i>per primam</i>
11	743824	5/22/44	Whipple	Spleen collaterals Splenectomy	Closed	Hemostasis satisfactory Removed 3rd day No bleeding Wound ready to graft 16th day
12	Beth David 44/1849	5/24/44	Bancroft	Scar tissue leg Releasing incision 20 cm long down to muscle	Open (Leg ulcers)	Hemostasis satisfactory Removed 3rd day No bleeding Wound ready to graft 16th day
13	737472	5/25/44	Hanford	Liver Punch biopsy	Closed	Hemostasis satisfactory Healed <i>per primam</i>
14	747716	5/26/44	Whipple	Gallbladder bed	Closed	Hemostasis satisfactory Healed <i>per primam</i>
15	747707	5/27/44	Blakemore	Periaortic Occlusion aortic aneurysm abdominal	Closed	Hemostasis satisfactory Healed <i>per primam</i> Some ecchymosis
16	747805	6/3/44	Blakemore	Periaortic Wiring aortic aneurysm, abdominal	Closed	Died, cardiac failure 24 hours No autopsy
17	738386	6/3/44	Mount	Sagittal sinus Opening sagittal suture	Closed	Hemostasis satisfactory Wound healed 4th day

four, wounds were closed which otherwise would have had to be left open and from which the packing would subsequently have had to be withdrawn. In three biopsy wounds—two liver and one sternal marrow—it took the place of muscle, which would otherwise have been used, and was considered fully as satisfactory, if not more so. In three oozing gallbladder beds it was a convenience but probably not a necessity. The other cases constitute scattered clinical trials. The complete list is to be found in Table V.

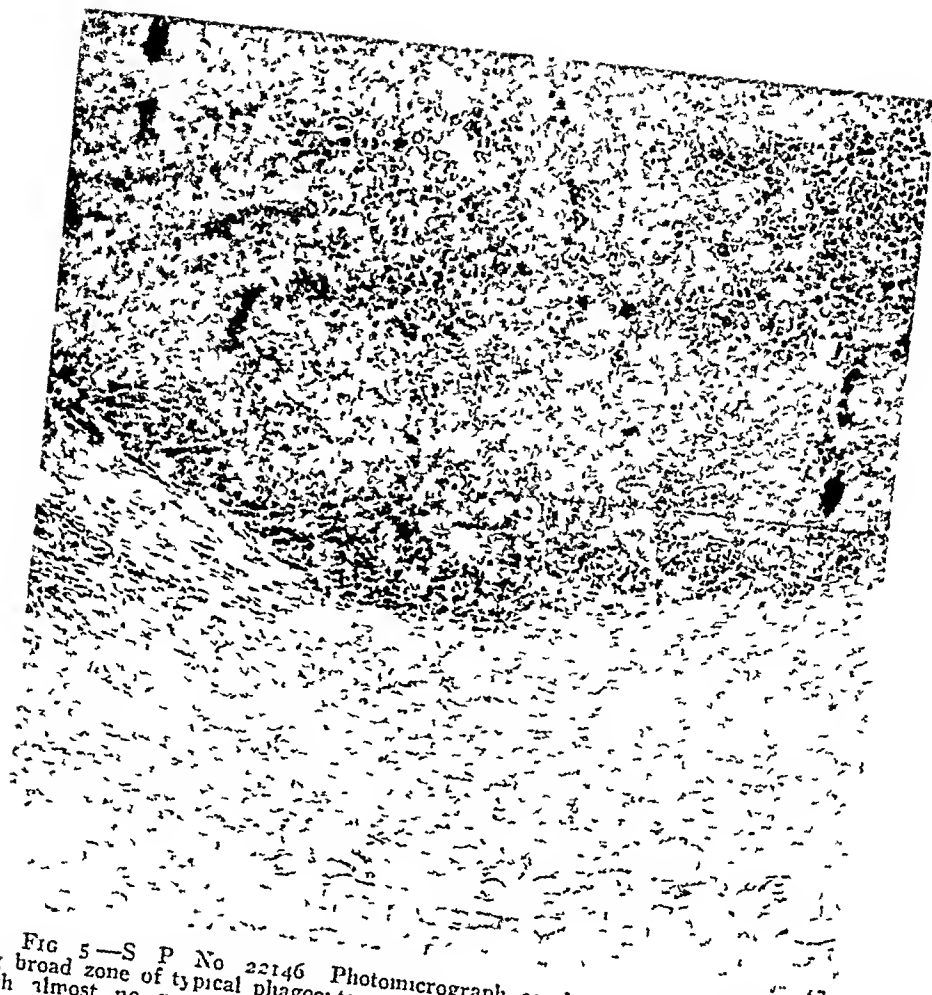


FIG 5—S P No 22146 Photomicrograph 31 days after operation, showing broad zone of typical phagocytes immediately adjacent to kidney parenchyma, with almost no granulation tissue (Low power)



FIG 6—S P No 22220 Photomicrograph showing remnants of oxidized gauze, above, persisting in kidney wound 30 days after packing. In this case few phagocytes are seen, and multinucleated foreign body giant cells are present, with considerable cicatricial tissue





FIG 7—S P No 22220 Photomicrograph showing site of "sandwich" packing on surface defect of spleen 30 days after operation. The spleen shows almost no scarring. There are typical phagocytes in scar tissue, above binding the omentum to the spleen. The gauze has been entirely absorbed.

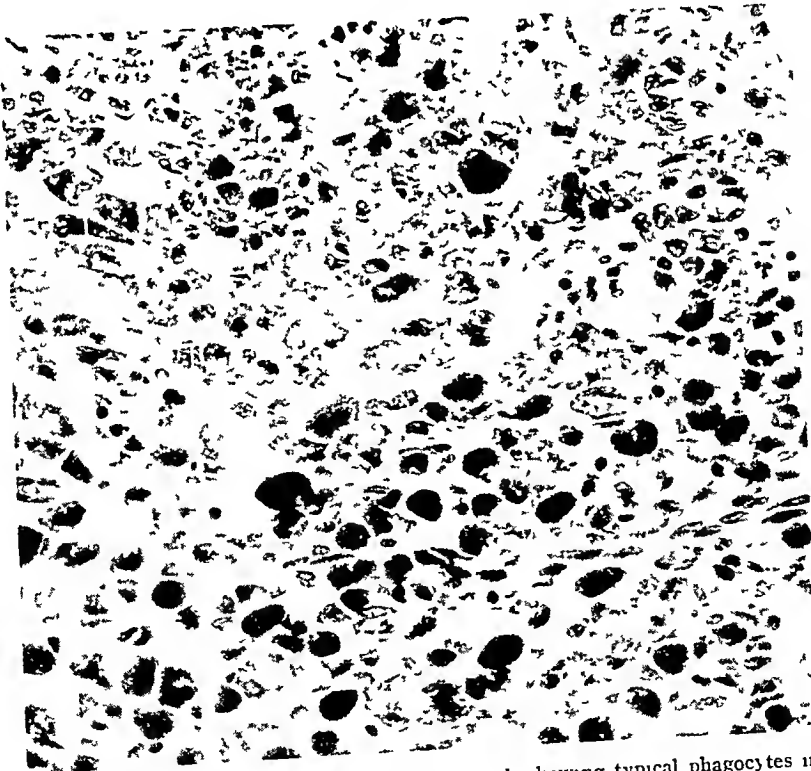


FIG 8—S P No 22220 Photomicrograph showing typical phagocytes in the very small zone of thickening in the omentum 30 days after oxidized gauze sponge implant. No cyst was formed. The gauze was completely absorbed.

# HEMOSTASIS WITH ABSORBABLE GAUZE



Fig 10—S P No 22312 Photomicrograph showing oxidized gauze in thyroid, 14 days after operation. In some parts—left, the gauze lies, except for artefact, against thyroid parenchyma with almost no reaction. On the right there is a zone of phagocytes between the picking and the thyroid



Fig 9—S P No 22314 Photomicrograph showing wall of omental cyst 37 days after oxidized gauze sponge implant. The surface of the omentum is shown as the lower border. The lining appears above as several layers of phagocytes. The fluid content shows few cells

It will be seen in the table of clinical cases that there is one case in which hemostasis was obviously not secured and which was complicated by an hematoma and pleurisy with effusion. This case, together with the four cases in which packing of some sort was imperative, two closed and two open, are analysed in detail.

## ANALYSIS OF CLINICAL CASES

**Case 1**—History No 633513 M D, female, white, age 38 Dr Byron Stookey. Four previous attempts by other surgeons to relieve pain by division of the sensory root of the right trigeminus. Persistence of symptoms.

**Operation**—April 10, 1944. Fifth craniotomy. Scar tissue was encountered which, when slightly manipulated after root section had been completed, gave way, and sudden bleeding occurred, thought to come from the internal carotid. This was controlled by vaselined gauze packing. The wound was drained at the lower angle.

**Course**—There was no febrile reaction following this procedure.

**Operation**—April 13, 1944. Wound opened. Packing removed. There was fresh bleeding of the same type as at the original procedure three days earlier. This was controlled by packing with formaldehyde sterilized oxidized gauze, Parke, Davis 6-hour oxidation No 098630. Three strips were used, 8 x 6 cm each, folded in four. The first strip was impregnated with 1 cc of sodium penicillin 5,000 units. Bleeding was completely controlled by the first two pieces of packing. The third piece was used as reinforcement, but perhaps added unnecessarily to the bulk—something probably to be avoided. The wound was closed.

**Course**—Patient ran no fever. There was swelling at the lower extremity of the wound, the site of the original drainage, first observed at the first dressing on the fourth postoperative day, when all sutures but one were removed. There was no redness in the swollen area, which was in the anesthetic zone following root section.

On the sixth day there was spontaneous discharge of thin, brown fluid from the lower angle of the wound, with particles of black, oxidized gauze. Culture of the discharge on the seventh day yielded organisms of the *B subtilis* group and coagulase-negative micrococci—no pathogens. The sinus continued to drain small amounts of sticky fluid showing almost no cells on smear. On May 1, 1944, 17 days after secondary packing with oxidized gauze, the patient had a small, unhealed, granulating area in the lower angle of the wound with practically no residual swelling or discharge. On May 15, 1944, a month after operation, the wound was entirely healed.

**Case 3**—History No 741879 N Y, male, Japanese, age 55 Dr George H Humphreys. Atypical history. Roentgenograms showed possible mediastinal mass.

**Operation**—April 22, 1944. Right lower lobe lobectomy for carcinoma of lung. There were many adhesions to the chest wall and to the diaphragm. The lower lobe was largely occupied by a tumor which, on quick frozen-section, appeared to be a carcinoma. Lobectomy was, therefore, carried out.

In this procedure part of the diaphragm was resected, and the liver immediately beneath was torn. There was bleeding which could not be controlled by ligature, and which required packing. Five pieces of oxidized gauze, 8 x 6 cm each, Parke, Davis No 098630 sterilized by formaldehyde, were folded to form a compress about 4 x 2 cm. This was applied to the surface of the liver, and the diaphragm closed over the packing with three interrupted black silk sutures. The oxidized gauze rapidly turned black, and hemostasis was considered satisfactory. Sulfadiazine powder was blown into the cavity and the wound closed, with an intercostal catheter for drainage.

**Course**—The patient had a gratifyingly smooth course. The intercostal catheter was removed on the third postoperative day, with no unusual discharge recognized. All stitches were removed on the sixth postoperative day, and the wound appeared healed.

The patient was afebrile from the sixth postoperative day. On May 1, 1944, the ninth postoperative day, roentgenograms showed some fluid at the right base, less, if anything, than one would expect under the circumstances.

**Case 5**—History No 639170 A P, male, white, age 36 Dr George H Humphreys. A case of essential hypertension admitted for a left dorsolumbar sympathectomy, to be done in two stages.

**Operation**—May 4, 1944 Through a paravertebral hockey-stick incision, cutting the diaphragm and dissecting the pleura forward off the mediastinum, the sympathetic chain was exposed along the lower dorsal vertebrae. Bleeding was encountered from the intercostal vein in the ninth interspace, which could not be controlled by clamping because of poor exposure. Bleeding was controlled by one 4 x 8 cm oxidized gauze sponge, Parke, Davis No 098630, folded into a square approximately 15 cm square, which was pressed into the intercostal space and held in place digitally until the gauze had become black and bleeding had been controlled. For a period of about 15 minutes thereafter no obvious bleeding occurred from the site. The gauze remained stuck without suture. Wound closed without drainage.

**Course**—At the first dressing, seven days after operation, the wound appeared well healed. All sutures were removed on the eighth day. The patient was never entirely afebrile, but was apparently doing well until the fourteenth day, when he began to run a spiking temperature, to complain of pain in the posterior part of the wound, and to cough. Roentgenograms of the chest on this day showed pleural effusion, and swelling was also noted in the posterior portion of the wound. Aspiration, extrapleural in the eighth interspace, yielded 40 cc of thick bloody fluid. On the nineteenth day a second aspiration in the tenth interspace, extrapleural, yielded 300 cc of ropy, slightly purulent old blood, with a faint fishy odor.

Thoracenteses on the twenty-seventh, thirty-second, and thirty-fourth postoperative days yielded 1,350, 1,350, and 250 cc, respectively, of clear, slightly blood-tinged pleural fluid. The patient was given sulfadiazine. On the thirty-fourth day the extrapleural collection was tapped again, and 150 cc of thick, grumous, brownish-red fluid was obtained. All cultures were negative, but on the thirty-fourth day the extrapleural pus showed an *hemolytic Staphylococcus aureus* on culture.

**COMMENT**—This case is given in detail because it is a failure in hemostasis. Doctor Humphreys is now of the opinion that with bleeding of this magnitude the gauze should have been held in place by suture, and that the hematoma cannot be attributed to a failure of the material but to an error in the way in which it was used. The interpretation of this complication is not altogether clear, the febrile reaction having been somewhat greater than one would expect with a simple hematoma, even though large and a sterile pleural effusion. Very possibly the sulfadiazine therapy was responsible for the failure of growth of organisms, and the infection, in view of the repeated aspirations and the initial absence of organisms or pus, should probably not lead to suspicion that the gauze was contaminated.

**Case 9**—History No 738341 N C, female, white, age 64 Dr H D Harvey. A case of infection of the foot of three months duration in a woman with arteriosclerosis and mild diabetes. In an effort to save at least part of the foot repeated attempts were made to secure adequate drainage. This included removal of the first three toes, and wide opening down to the plantar fascia. The infection was not completely controlled and although there was considerable healing, a sinus led to sloughing plantar fascia and flexor tendons.

**Operation**—May 13, 1944 Revision of drainage. The sinus tract was laid open

down to the deep slough. The granulation tissue was edematous and there was profuse bleeding from many small vessels. Oxidized gauze, Parke, Davis No 098630, was packed into the wound. Bleeding continued, but stopped when pressure was applied. A pressure dressing, therefore, was used.

*Course*—May 14, 1944. First day postoperative. The gauze was gelatinous and came away readily. There was no further bleeding. The slough continued to separate, but in the course of three weeks the sinus had again closed prematurely and drainage was inadequate.

*Operation*—June 5, 1944. Revision of drainage. The sinus was opened. There was dense scar tissue around it from which bleeding was brisk. One vessel of considerable size was encountered and transfixation and ligature were not feasible. Packing was, therefore, imperative. Oxidized gauze, Parke, Davis No 098630, was used, and the wound was filled to the surface with gauze which was allowed to overlap the skin edges slightly to prevent sticking of the dressing.

*Course*—June 6, 1944. First day postoper. The gauze was black and the surface dry. There was no marked redness around the wound. The patient said she had had pain during the night. The outer dressing was practically dry. The packing was not disturbed.

June 7, 1944. Second day postoperative. Dressing. The gauze was still dry on the surface and could be removed almost in one piece. A few fragments remained in the wound. These could be picked up with forceps, and although somewhat gelatinous, still had fibrillar structure. No bleeding followed removal of the gauze. The wound edges had been kept apart satisfactorily for the 48 hours. There was no retained exudate in the wound, although there was slough, as expected, in the depths.

**Case 13**—Beth David Hosp No 44/1849. A C, male, white, age 55. Dr Frederic W Bancroft.

*History*—In November, 1942, the patient had a bilateral herniorrhaphy. After discharge from the hospital he developed pain in the right knee and the whole leg became swollen, presumably a phlebitis. After the pain subsided, the leg remained swollen and ulceration began June, 1943.

*Past History*—Neisserian infection, 1939. Otherwise irrelevant.

*Physical Examination*—Right leg markedly swollen below the knee with a wide zone of brown discoloration and superficial ulceration, two ulcers as large as 5 cm each. Urine analysis showed no sugar. Blood sugar 100 mg per cent, W B C 11,800, polys 64 per cent.

The patient was treated by rest, elevation, and dressings for ten days preoperatively.

*Operation*—May 24, 1944. Ligation of saphenous bulb. Release of scar tissue. An incision about 20 cm was made on the medial aspect of the calf and deepened through dense scar tissue through the deep fascia and the sheath of the muscles. The scar tissue was exceedingly thick, and there was no marked gaping until the deep fascia was cut. The wound then gaped widely, and obvious bleeders were controlled by catgut ligature. There was ooze from all the surfaces of the scar tissue and, accordingly, four pieces of oxidized gauze, Parke Davis D-2340-C, were laid on the wound surface. As a test of the material two cotton pledgets, Parke, Davis D-2339-C, were placed in the lower angle of the wound. It was Doctor Bancroft's impression that the material was hemostatic.

Vaselined gauze packing was then placed in the wound and a light pressure dressing applied. Neither the packing nor the pressure was so much as Doctor Bancroft has used in the previous dozen or so cases of this operation of his own devising.

*Course*—May 25, 1944. First day postoper. Doctor Bancroft reported by telephone that the patient's bandages were dry in contrast to the usual postoperative oozing of previous cases.

## HEMOSTASIS WITH ABSORBABLE GAUZE

May 27, 1944 Third day postoperative First dressing There was, according to Doctor Bancroft, less blood on the dressing than usual The gauze was soft, somewhat slimy on the under surface, and could be scooped out of the wound Nowhere was it stuck, and no bleeding occurred except where the vaselined gauze was stuck on the wound edges It would have been better to cover the wound edges with the oxidized gauze Doctor Bancroft felt that the hemostasis had been unusual, and the dressing satisfactory The wound looked somewhat brown Vaselined gauze dressing

May 30, 1944 Sixth day postoperative Wound still brownish Little exudate

May 31, 1944 Seventh day postoperative Wound still brownish Little exudate  
Acriflavine wet dressing Dressed thereafter q 2 d with acriflavine Wound ready for grafting June 9, 1944, 16 days postoperative

COMMENT—In previous cases of leg ulcer and deep scarring, which Doctor Bancroft has treated by one or more releasing incisions, he has found the wound suitable for grafting some time between the tenth and twenty-first postoperative day This case, ready for grafting on the sixteenth postoperative day, is in line with the others In his opinion, use of the oxidized gauze facilitated hemostasis and did not hinder repair

### SUMMARY

This report is submitted at this time in the hope that further clinical trial of the material will be made in other hospitals, so that, if it proves useful, its availability to the armed forces may be expedited. It appears to have sufficient hemostatic properties when used dry so that combination with thrombin is probably unnecessary, possibly undesirable It is hoped that the investigators who are familiar with the control of hemorrhage with thrombin and cellulose as a carrier (Putnam, Ingraham and Bailey, Cronkite, Deaver, and Lozner), will try the cellulose without the thrombin, as the reverse has already been tried Possibilities of impregnation of the material with antibacterial substances naturally suggest themselves This field needs further study, but our own preliminary work with penicillin suggests an incompatibility Work is still in progress on the development of nonirritating membranes, and absorbable suture, or at least ligature, material It is too early to evaluate these results

At the risk of being pedantic, we close with a warning This material, even though soluble and *relatively* nonirritating *is a foreign body* in the tissues and remains as such often for several days It should be used, at least in wounds which are closed without drainage, in as small quantity as possible It is not a substitute for meticulous surgery, and surgical principles must not be violated in its use

We are indebted to Miss Daisy Mapes, R N, for her assistance in all of the animal experimental work, her close scrutiny of the material, and the results of its application

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# LEIOMYOMA OF THE JEJUNUM

INTERMITTENT MELENA OF FOURTEEN YEARS DURATION,  
AND FATAL HEMORRHAGE

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LEIOMYOMA OF THE SMALL INTESTINE IS uncommon Raiford,<sup>15</sup> in 1931, collected 82 cases of small bowel tumors from the records of the Johns Hopkins Hospital Only three cases of this total were leiomyomata, two of these occurring in the jejunum and one in the ileum In a later report, Raiford,<sup>16</sup> from a study of the findings in 11,500 autopsies and 45,000 surgical pathologic specimens, was able to find a total of 986 cases of tumors, both benign and malignant, of the gastro-intestinal tract Of these, tumors of the small intestine constituted 8.9 per cent, the benign tumors of the small intestine making up 23.8 per cent of all the benign neoplasms of the gastro-intestinal tract

Rankin and Newell,<sup>17</sup> in 1933, reported 95 instances of neoplasms of the small bowel, 35 of these were benign, 11 of this group being leiomyomata A year later, Moore and Schmeisser,<sup>13</sup> in a review of the literature, were able to cull only 46 case reports of small intestine leiomyomata Of this group, nine occurred in the duodenum, 15 in the jejunum, 19 in the ileum, and the site in four instances was not specified, in only one case were multiple tumors present In 1937, Smith<sup>19</sup> was able to collect 513 cases of leiomyomata of the gastro-intestinal tract Of these, 50 occurred in the esophagus, 321 in the stomach, 109 in the small intestine, and 33 in the colon He found, in reviewing the protocols of 36,000 autopsies at the Philadelphia General Hospital, 33 cases of gastro-intestinal tract leiomyomata, eight of which arose from the small bowel Two years later, Horsley and Keasbey<sup>7</sup> reported 15 additional cases of leiomyomata of the small bowel Morison,<sup>14</sup> in an analysis of the biopsy and autopsy material of 13,139 patients at Queen's University, at Belfast, found 21 benign tumors of the small intestine, of which two were leiomyomata of the ileum In 1942, Weber and Kirklin<sup>20</sup> analyzed the material at the Mayo Clinic over a 32-year period and gathered a total of 108 malignant small bowel tumors and 41 benign neoplasms of the small intestine, of the latter group, myomata constituted 14 cases, eight of these being found in the duodenum, four in the jejunum, and two in the ileum Since then, additional case reports have appeared sporadically in the literature <sup>2, 6, 8, 10, 18</sup>

There is no marked sex predilection for leiomyomata of the small bowel, although, as for tumors in general, males may be slightly in the fore <sup>16</sup> The majority of benign tumors of the small bowel occur between the ages of 30 and 40,<sup>17</sup> but the age incidence is wide, ranging from 13 to 79 <sup>13, 16</sup> One case in a child, age two, has been reported <sup>12</sup>



In size, leiomyomata of the small intestine may vary from that of a pea to that of a large grapefruit. A tumor weighing 1,500 grams has been reported.<sup>4</sup>

Leiomyomata of the small bowel are most common in the ileum. The next most frequent site is the jejunum, while the duodenum is only rarely affected.<sup>13, 16</sup>

Pathologically, leiomyomata of the small intestine have been classified, according to site in the bowel wall, as principally submucosal or principally subserosal, 70 of the 109 cases of Smith<sup>19</sup> falling into the latter group. Microscopically, leiomyomata are made up of whorls and interlacing bundles of smooth muscle cells, a varying amount of fibrous supportive stroma being present. Necrosis, hyaline degeneration, and hemorrhage into the tumor mass have been described.<sup>10</sup>

The incidence of malignant change in leiomyomata of the small intestine seems to be surprisingly high. According to Klopp and Crawford,<sup>11</sup> malignant change occurs in from 15 to 20 per cent of small intestinal myomata, and Smith<sup>19</sup> states that metastases or recurrences have occurred in 16 per cent of those leiomyomata of the subserosal type, no metastases, however, have been reported in leiomyomata of the submucosal variety. These findings are in striking contrast to the relatively low incidence of sarcomatous change in the histologically comparable leiomyofibroma of the uterus, which is between somewhat less than 1 per cent<sup>3</sup> and 2.5 per cent.<sup>5</sup>

Clinically, not all myomata of the small intestine give rise to symptoms. In Raiford's series of benign small bowel tumors,<sup>16</sup> 46 per cent were encountered as an incidental finding at autopsy, and only 18 of the 35 cases catalogued by Rankin and Newell<sup>17</sup> had symptoms referable to the lesion. However, of the 109 cases reported by Smith,<sup>19</sup> in only 15 instances was the lesion discovered as an incidental finding at operation or autopsy, the other cases having given rise to definite clinical complaints.

The two outstanding clinical features of the reported cases of leiomyomata of the small bowel are mechanical intestinal obstruction and enterorrhagia. In those tumors which are for the most part submucosal, the commonest presenting finding is intestinal obstruction secondary to intussusception, repeated episodes being not uncommonly observed. Intestinal obstruction was observed in 27 of the 39 cases of myomata of the submucosal variety reported by Smith.<sup>19</sup> Of those tumors which extend chiefly subserosally, the principal clinical feature is, in most instances, gastro-intestinal hemorrhage, repeated episodes of melena being found in an appreciable number of instances. Smith<sup>19</sup> reported gastro-intestinal hemorrhage in 22 of his 70 cases of myomata of the subserosal type, and hemorrhage has been prominent in cases reported by others.<sup>1, 4, 9, 10, 13</sup> Other less frequent clinical manifestations of small intestinal myomata are evidences of peritoneal irritation secondary to acute necrosis of the tumor mass or volvulus,<sup>4</sup> the presence of a palpable mass in the abdomen,<sup>12, 14, 19</sup> recurrent ulcer-like distress,<sup>17, 18, 19</sup> frank peritonitis due to rupture,<sup>4, 19</sup> and vague, nondescript indigestion.<sup>19</sup>

Roentgenologic examination, in many instances, is of assistance in the

diagnosis of tumors of the small bowel, but this is by no means true in all cases. There are several reasons for the failure in some cases to diagnose the presence of a small intestinal tumor roentgenographically. Perhaps the most important of these is the failure of the clinician to suspect the presence of a lesion of this type, and, as a consequence, the roentgenologist, not being forewarned, does not look for evidence of the lesion with sufficient care or sufficient persistence. Secondly, subserosal tumors, which accounted for two-thirds of the cases of myoma reported by Smith,<sup>10</sup> are unlikely to produce a marked subtraction defect in the silhouette of the barium-filled small bowel. Thirdly, due to the extensive overlapping of small bowel shadows, a defect, even if present, may easily be overlooked. Repeated progress-meal studies and, in some cases, the introduction of barium directly into the jejunum through a tube are prerequisites for adequate roentgenologic visualization of small intestinal neoplasms. If obstruction due to a tumor of the small bowel is present, plain films of the abdomen will reveal the usual roentgenologic evidences of dynamic ileus, and in those cases of colonic involvement by an intussuscepting mass in the small intestine barium enema studies are of value.

We have recently had the opportunity to study a patient with a leiomyoma of the jejunum who had 20 known episodes of melena over the course of 14 years. This represents, to our knowledge, the most protracted history of episodic bleeding and the greatest number of individual hemorrhages to be reported in a case of leiomyoma of the small intestine. We are, therefore, describing this case in detail.

**Case Report**—M. P., a Jewish male, age 53, was first admitted to the Graduate Hospital under the care of Dr. H. L. Bockus, November 30, 1941, complaining of the passage of several tarry stools that morning. His history dated back to 1930 when, for the first time, he noticed that for a period of three or four days his stools were black. Four months later, a similar episode occurred. Roentgenologic examination at that time revealed no evidence of ulceration in the upper gastro-intestinal tract. The patient did well for a period of eight months before melena once more was noted. A second barium progress-meal revealed changes which were somewhat suggestive of peptic ulcer. During the following two years the patient experienced two more episodes of bleeding. During this time he never presented any clinical complaints suggestive of active peptic ulcer. However, in 1933, a gastro-enterostomy was performed, although, at operation, no ulcer of the stomach or duodenum could be demonstrated. Five months later melena of several days duration again appeared, and during the next two years this recurred sporadically at intervals of five to six months. In 1936, the patient developed marked melena which was associated with the vomiting of dark brown material. Because his hemoglobin level had dropped to 20 per cent of normal, hospitalization and repeated transfusions were necessary. A progress-meal following this episode of intestinal bleeding revealed no evidence of ulcer formation. During the next four years melena occurred at least six times, the longest free interval having been 13 months. Although the patient had never had any abdominal discomfort prior to surgery, from the time of the gastro-enterostomy he experienced occasional episodes of epigastric distress characterized by food and alkali relief, at no time did he have day-to-day discomfort. His epigastric complaints coming on capriciously and sporadically. He was gastroscoped in 1939, and no ulcer was seen. In December of 1940, he consulted Dr. H. L. Bockus for the first time. At that time

physical examination was nonrevealing save for a blood pressure of 160/90. His stools were negative for occult blood. The erythrocyte count was 4.1 million cells per cu mm, with 11 Gm of hemoglobins, and the leukocyte count was 7500 cells per cu mm, with a normal differential. The platelets numbered 127,480 per cu mm, bleeding time was 30 seconds, and the Quick prothrombin time was 80 per cent of normal. The gastric analysis revealed no free acid in the first five specimens, bile being present in each extraction, a free acid of 13 units, with a total acid of 28 units, appeared in the sixth extraction. Progress-meal studies revealed no evidence of esophageal varices, an estimated 90 per cent of the barium meal was passing through a well-functioning gastro-enterostomy stoma, no ulcerative lesion of the stomach or duodenum was demonstrated, and the small intestinal loops were considered normal after careful survey. A barium enema study was negative. The Rumpel-Leede test was negative, there was no pathologic urobilinogenuria, and the serum bilirubin was within normal limits. Gastrosopic examination revealed no evidence of bleeding points or ulceration either in the body of the stomach or the well-visualized stoma. The patient was placed on a modified ulcer regimen, and did well for one year, except for occasional mild and transient episodes of epigastric discomfort. On November 30, 1941, however, melena once more recurred, and the patient was hospitalized.

Physical examination on admission revealed no evidences of shock. The blood pressure was 160/85. There was no tachycardia or jaundice, and the liver and spleen were not palpable. A small amount of tarry fecal matter was present in the rectum, but no cherry red blood was seen. Blood studies on admission revealed an erythrocyte count of 5.25 million cells per cu mm, a hemoglobin of 12.5 Gm, and a leukocyte count of 11,100, with 78 per cent neutrophils. There were 214,000 platelets per cu mm. No further tarry stools were passed following admission. Patient was treated expectantly, and, December 6, 1941, he was discharged on his previous dietary regimen.

Melena recurred once more in September, 1942, and on the eighth of that month, he was readmitted to the Graduate Hospital. Physical examination at that time revealed a blood pressure of 128/90. The liver and spleen were not palpable, and tarry material was present in the rectal ampulla. His erythrocytes numbered 4.0 million cells per cu mm, with a hemoglobin of 12.5 Gm. The total leukocyte and differential counts were within limits of normal. There were 168,180 platelets per cu mm, and the prothrombin time was 95 per cent of normal. He was treated with hourly feedings, and, September 14, 1942, he was discharged.

He was followed regularly and had no recurrences of his melena until September, 1943, when, while in another part of the country, he suddenly developed another episode of bleeding, which was associated with hematemesis. Because of the severity of his gastro-intestinal hemorrhage he was hospitalized, and on seven occasions transfused. He made a good recovery and was discharged after a month's stay in the hospital. Laboratory studies during the following winter revealed an erythrocyte count of 5.16 million cells per cu mm, a hemoglobin of 14 Gm, a leukocyte count and differential within normal range, a platelet count of 304,400 per cu mm, prothrombin time of 61 per cent of normal, no retention of dye in 30 minutes with the 2 mg dose of bromsulphalein, and a gastric acidity of 20 units of free acid and 40 units of total acid. Once more a progress-meal study revealed no evidence of esophageal varices or upper gastro-intestinal tract ulceration.

On March 21, 1944, the patient developed an episode of mild postprandial discomfort localized in the epigastrium, and accompanied by borborygmi. Several hours later he had a passage of liquid fecal material of tarry nature. He became weak and felt chilly, but syncope did not occur. That night he was admitted to the Graduate Hospital for the third time. On examination, the patient was apprehensive, and his skin and mucous membranes were somewhat pale. The blood pressure was 150/90. The abdomen revealed no abnormalities. The red cell count was 4.24 millions per cu mm, with a hemoglobin of 12 Gm. During the three days following hospitalization melena continued, and despite

## LEIOMYOMA OF JEJUNUM

repeated transfusions of whole blood and plasma the blood pressure fell to 82/60, the erythrocyte count decreasing to 3 12 million cells per cu mm, with a hemoglobin of 49 per cent, and a hematocrit of 23 per cent. The patient went into shock late in the afternoon of March 24th, and died several hours later. Autopsy examination was performed one hour after death.

*Autopsy*—Examination revealed marked pulmonary edema. Save for an extreme degree of paleness the liver and spleen showed no abnormalities. The esophagus was normal throughout, and no varices were present. The stomach was normal in size and

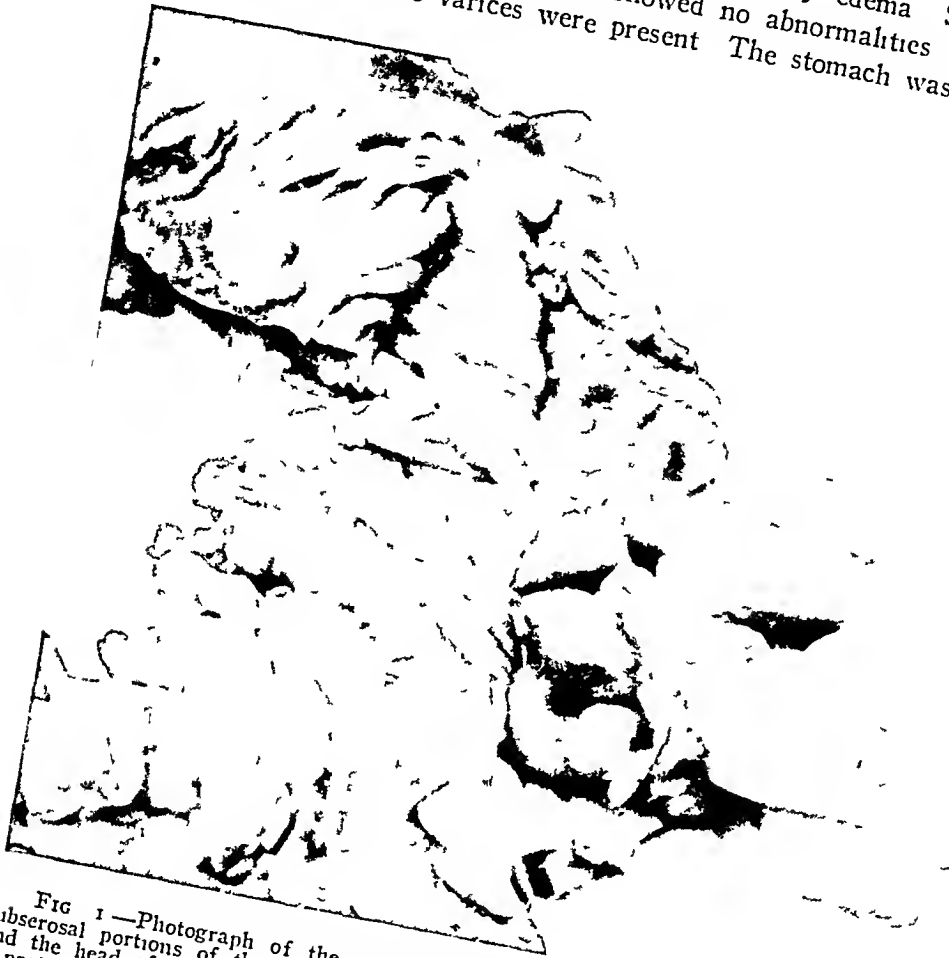


Fig. 1—Photograph of the gross specimen showing both the submucosal and the subserosal portions of the leiomyoma. Sections have been taken for microscopic study, and the head of the pin used to hold the specimen together should not be mistaken for a part of the lesion.

shape and contained small amounts of bile-stained material, the mucosa showed no injection of erosion, and careful search revealed no scars or ulcerations. A small polypus, 2 to 3 mm in length, was found along the greater curvature in the pyloric portion of the stomach. The gastro-enterostomy stoma was patent and easily admitted a thumb, no tumor or ulceration was found in or about the stoma. The duodenum showed no abnormalities, and the distal and proximal loops of the enterostomy were entirely negative. No blood was present in the stomach, duodenum, or distal or proximal jejunal loops.

Eight inches distal to the enterostomy stoma, in the wall of the distal jejunum, was a firm, somewhat nodulated tumor mass. It was the size of a walnut and was composed of pale, firm pinkish tissue. One-half of this lesion extended submucosally between the layers of the mesentery. The mucosal surface of the tumor was smooth and glistening, and no prominent vessels or bleeding points were to be found on careful inspection. The tumor showed no evidence of ulceration or necrosis. Several centimeters distal to the lesion bright red blood was encountered in the lumen of the jejunum. A short distance

further the material within the lumen became tarry, and the remainder of the small bowel and the entire large bowel was filled with blackish semiliquid fecal material. With the exception of the tumor mass in the upper jejunum no other lesions could be found in the entire gastro-intestinal tract which could explain the melena.

Histologic examination of the tumor tissue revealed the mass to be made up of interlacing bundles and whorls of smooth muscle. The nuclei were vesicular and spindle-shaped, no mitotic figures were seen. Sections stained for connective tissue by Mallory's

FIG 2

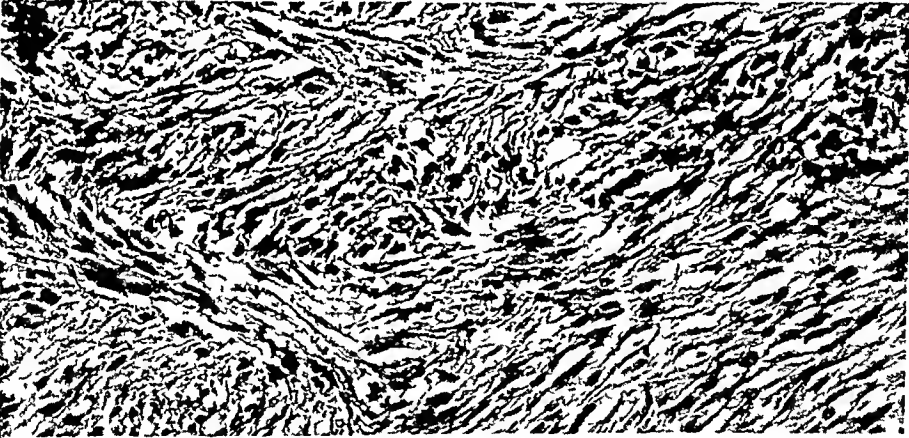
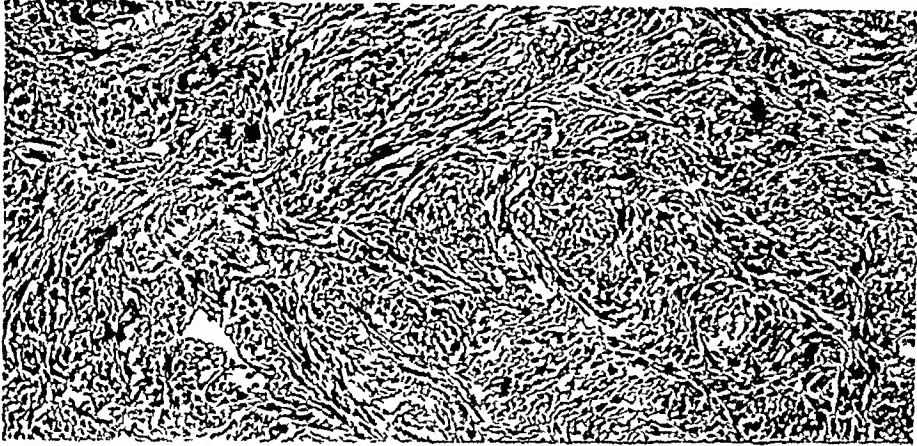


FIG 3

FIG 2—Photomicrograph of the tumor showing the interlacing bundles of smooth muscle in longitudinal section and in cross section (Hematoxylin and eosin X150)

FIG 3—A higher powered view of a portion of the section seen in Figure 2. The spindle shaped nuclei are prominent (Hematoxylin and eosin X330)

method revealed only a moderate amount of fibrous supportive stroma. *Pathologic Diagnosis* Leiomyoma of the jejunum

**DISCUSSION**—This case represents an instance of repeated episodes of melena over the course of a considerable number of years, and a fatal termination from bleeding into the gastro-intestinal tract in a patient who had a benign tumor of the jejunum. It is of interest that ulcer disease, though suspected, had never been demonstrated conclusively, and that a gastro-enterostomy had been injudiciously performed. In all likelihood, had the presence of

a tumor of the small bowel been strongly considered and appropriate surgical exploration advocated, the patient might not have died

This case emphasizes the fact that the presence of small intestinal neoplasms is much too infrequently suspected. The diagnosis of tumors of the small bowel, both benign and malignant, rests upon a high index of suspicion. The possibility of a neoplasm of the small intestine should be considered in any patient who has repeated episodes of melena in the absence of any demonstrable lesion in the upper gastro-intestinal tract or colon, and in any patient with repeated episodes of partial or complete obstruction in the small bowel. In such instances, despite the absence of roentgenologic demonstration of the lesion, celiotomy is indicated. Since the ratio of benign to malignant tumors is much greater in the small intestine than in other parts of the gastro-intestinal tract, surgery for small bowel tumors should, on the whole, afford a better ultimate result than can be expected for tumors of the esophagus, stomach, or colon.

#### SUMMARY

1 The incidence, pathologic characteristics, and clinical features of leiomyoma of the small intestines are reviewed.

2 A case of a patient with a leiomyoma of the jejunum who had 20 known episodes of melena over a 14-year period, with a fatal hemorrhage, is reported.

3 The necessity for a high index of suspicion for tumors of the small intestine is pointed out.

We wish to thank Dr. H. L. Bockus for permission to report this case.

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# RETROGRADE JEJUNOGASTRIC INTUSSUSCEPTION THROUGH A SUBTOTAL GASTRECTOMY STOMA

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IN 1935, Ducey and McNamara<sup>1</sup> reported a case of retrograde jejuno-gastric intussusception through a gastro-enterostomy stoma. In a brief survey of the literature the authors found 36 instances of this rather unusual sequela of surgery for relief of peptic ulcer.

The recently encountered case of retrograde jejunogastric intussusception, which forms the basis of this report, was similar in all respects to the one previously described by these authors, with the exception that in this case intussusception occurred through a partial gastrectomy stoma, in the earlier case through a gastro-enterostomy stoma. This fact is of special interest because in recent years gastrectomy has replaced gastro-enterostomy almost universally as the operation of choice for relief of ulcer or cancer. It is believed that this is the first case recorded in which jejunogastric intussusception occurred through a partial gastrectomy stoma.

**Case Report**—A L, white, male, age 50, gave a history of chancre 20 years ago. He had had inadequate antiluetic treatment, and tabes dorsalis had developed. He complained of "stomach trouble" for many years, and five years prior to the present admission a gastro-enterostomy had been performed for relief of peptic ulcer.

On July 19, 1943, the patient was admitted to the hospital complaining of pain in the upper abdomen, especially severe before meals, and vomiting of "coffee ground" material. Occult blood was detected in the stools. The abdomen was tender. The clinical diagnosis was recurrent ulcer, probably in the gastro-enterostomy stoma, and operation was advised. The patient showed the ataxia of tabes dorsalis. Serologic tests of the spinal fluid were positive. The Wassermann test of the blood was negative.

At operation, September 9, 1943, two large marginal ulcers of the gastro-enterostomy stoma were found. The old anastomosis was excised and a subtotal gastrectomy was performed. The patient made an uneventful recovery and was discharged.

On November 17, 1943, the patient was readmitted, complaining of vomiting and pain in the upper abdomen. The pain was first experienced two weeks before admission (just one week after previous discharge). He had vomited persistently for the last four days. At the time of admission the patient was extremely dehydrated and semicomatose. The vomitus became fecal in type.

The heart and lungs were negative. The abdomen showed an old right upper paramedian scar and a recent but well healed upper midline incision. There was a fullness in the upper abdomen, indefinite in outline and apparently not the liver. The lower abdomen was flat. The patient rapidly lapsed into coma and expired. A tentative diagnosis of intestinal obstruction was made, but immediate surgery was deemed inadvisable due to the patient's extremely grave condition.

**Autopsy**—On opening the peritoneal cavity many old fibrous adhesions were noted. There was massive dilatation of the stomach, which measured 50 cm in length. The lower segment of the stomach had been resected. A retrograde jejunogastric intussusception of the efferent portion of the jejunum had occurred through the gastrectomy stoma.



There was marked dilatation of the afferent loop of the jejunum. The small intestine below the intussusception was collapsed.

On section of the stomach, it was noted that the intussuscepted portion of the jejunum formed a stovepipe-like sleeve, so that there was a double layer of intestine in the stomach. The length of the sausage-like mass in the stomach measured 25 cm, when stretched out it measured in excess of 50 cm. The greater part of the length of the jejunum found in the stomach was partially digested and gangrenous (Fig 1).

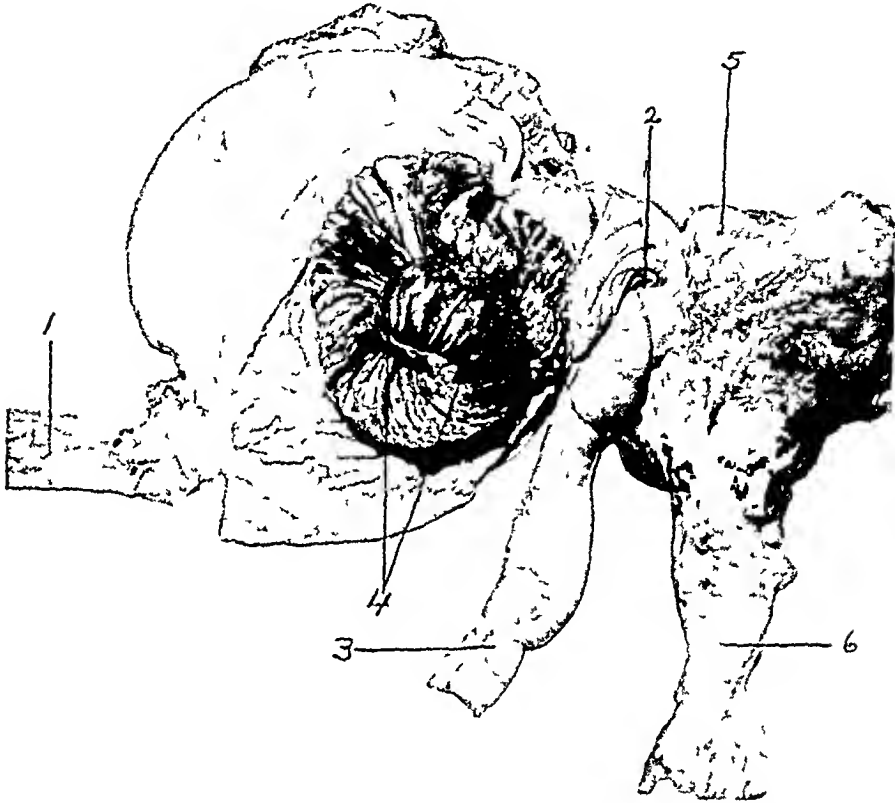


FIG 1—Necropsy specimen, posterior view. 1 Esophagus, 2 site of stoma, 3 efferent loop of jejunum, 4 telescoped loop of jejunum filling stomach, 5 blind end of duodenum, 6 pancreas.

There were many adhesions in the area of the stomach and around the blind end of the duodenum. The portion of the small intestine below the intussusception and the large intestine were grossly negative.

*Anatomic Diagnosis* Retrograde jejuno-gastric intussusception through an old partial gastrectomy stoma.

**DISCUSSION**—Ducey and McNamara (1937) found 36 cases of jejuno-gastric intussusception, and added a case of their own. Schackman (1940) notes additional cases by Bonomi (1937), Greenwood (1937) and Otero (1938). Schackman states that if a gastro-enterostomy has both an afferent and an efferent jejunal loop, three types of jejuno-gastric intussusception may occur. Type I—The afferent loop may intussuscept through into the stomach. Type II—The efferent loop may undergo retrograde intussusception and either stop short of, or pass through, the gastro-enterostomy stoma. Type III—Both afferent and efferent loops together may intussuscept through into the stomach.

Schackman reports a case of Type III in which a preoperative diagnosis of

jejuno gastric intussusception within a short time after onset of symptoms, and patient came to operation 15 hours later. The intussusception involving about 3.5 feet of red, congested jejunum was reduced. The gastro-enterostomy stoma was seen and appeared normal apart from a hemorrhagic area 0.5 x 0.5 inches, due to extravasated blood following mechanical congestion on the anterior surface of the anastomosis. No effort was made to anchor the jejunum. The patient made an uneventful recovery, and later by gastroscopy the gastro-enterostomy was demonstrated to function well.

Schackman stresses the necessity for early diagnosis leading to immediate surgery in these cases. From his study he finds that in Types II and III there is a 50 per cent mortality if operation is delayed more than 48 hours after onset of symptoms. Schackman summarizes "The condition should be considered if ever a patient has abdominal pain and vomiting, with or without hematemesis, coming on at any time after a gastro-enterostomy."

Chamberlain (1940) divides into two clinical groups the reported cases of retrograde intussusception of the jejunum into the stomach (a sequel following gastro-enterostomy) as follows:

"In one group the patients have a brief illness evidenced by epigastric pain and vomiting first of food, then of bile and finally blood. An epigastric tumor may be palpated above and to the left of the umbilicus. Visible peristalsis and upper abdominal rigidity are often present. The usual preoperative diagnoses have been high intestinal obstruction, a ruptured viscus, or an acute surgical abdomen. In this group the prognosis is grave and surgical intervention should be immediate.

The other group of patients is composed of those who maintain a state of chronic invalidism following a gastro-enterostomy for peptic ulcer. The characteristic symptoms beginning at any time from five days to 14, or more, years after operation are epigastric pain, nausea and vomiting which occur at irregular intervals and subside spontaneously. The author adds that in these patients, as in the case of chronic recurrent jejuno gastric intussusception through a gastro-enterostomy stoma which he reports, radiographic examination aids in establishing the diagnosis. In this unusual case the intussusception demonstrated repeatedly by fluoroscopic methods was not in evidence when celiotomy was performed about ten days later. The author states that the evidence is conclusive that the patient had a retrograde intussusception of the jejunum which spontaneously reduced itself. The clinical history suggests that this may have occurred many times before the lesion was found, and the history of occasional vomiting attacks subsequent to the operation suggests that it continues to occur.

The case which forms the basis of this report differs from the similar cases in the literature in that the intussusception occurred through a partial gastrectomy stoma rather than through a gastro-enterostomy stoma. It is also interesting that the intussusception occurred so soon after gastrectomy. The operation was performed September 19, 1943 and the first symptoms occurred about six weeks later. Bettman and Baldwin in their résumé noted that the

accident had occurred as early as one year and as late as 16 years after gastro-enterostomy. Due to the delay (two weeks) which intervened between the onset of the initial symptoms (pain and vomiting), and on return of the patient to the hospital the patient was almost moribund and was beyond the aid of surgery when seen. This stresses the importance of early diagnosis and immediate surgery in these cases.

#### SUMMARY

1 A case is presented in which retrograde intussusception of the jejunum occurred through a gastrectomy stoma.

2 It is important that the possibility of retrograde intussusception of the jejunum through the stoma be considered whenever suggestive symptoms, such as severe pain and bloody vomitus occur in a patient who has been subjected to gastro-enterostomy or subtotal gastrectomy.

3 An early diagnosis is important because immediate surgery constitutes the only hope, except in the chronic type as described by Chamberlin.

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# THE INFLUENCE OF ETHER, MORPHINE AND NEMBUTAL ON MORTALITY IN EXPERIMENTAL BURNS\*

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THE PRESENT COMMUNICATION deals with experiments showing that the early mortality following severe thermal injury is profoundly influenced by the type of sedation and anesthesia used. In the first paper of this series<sup>1</sup> the combination of nembutal and morphine used produced a good anesthesia during the injury itself, as well as a fairly prolonged sedation afterwards. Following the publication of this data, Dr Alfred Blalock wrote that he had repeated these experiments and had observed a much lower mortality, indeed, only two deaths occurred under 24 hours in a series of 12 experiments in which a thermal stimulus of 85° to 90° centigrade for 5 to 15 seconds, up to the axilla, was employed. With a similar degree of injury, our mortality was 100 per cent. The fact that he used a smaller dose of morphine without nembutal plus a short ether anesthesia during the burn stimulus suggested that the pronounced difference in mortality might perhaps be due to the type of anesthesia used. In order to study this supposition, a series of experiments were carried out in which a somewhat more severe burn stimulus (immersion up to the axilla at 100° centigrade for 10 seconds) was employed in a series of ten experiments each, various doses of morphine in combination with nembutal or ether were used in each group.

*Experimental Findings*—Table I records the essential findings, which indicate clearly the deleterious effect of morphine and nembutal, particularly the former, on the 24-hour mortality.

TABLE I  
INFLUENCE OF ETHER, NEMBUTAL AND MORPHINE ON 24-HOUR MORTALITY

No of Experiments	Agent Used and Dose		Ether during Burn	24-Hour Mortality
	Numbutal (i v ) mg /Kg	Morphine* mg /Kg		
10	30	6-10	0	100%
10	30	0	0	50%
10	0	6-10	yes	80%
10	0	3	yes	20%
10	0	0	yes	10%

\* These doses, because the dog is much less susceptible than men, are well within therapeutic range.

Hemoconcentration curves were obtained in these experiments, but only those in the three groups given ether are of significance. There was little difference in the two groups receiving both morphine and ether. However,

\* Aided by a grant from the Commonwealth Fund

the group anesthetized with ether, but without morphine, showed a higher peak both in the nine survivals and in the one fatality. From this, it may be inferred that morphine has little influence on the hemoconcentration in burns, if anything, it tends to decrease it. Its deleterious influence, therefore, must be connected not with the physical changes in the blood produced by the burn, but rather with a toxic effect on respiration or on some other vital function.

COMMENT—The deleterious effect of morphine on the mortality in experimental burns seems quite clear from the present findings. When ether was used during the burn stimulus, the mortality was lowest when no morphine was employed, but increased to 80 per cent when the dose of morphine was 6 to 10 mg per kilogram. The deleterious effect of nembutal with morphine is shown by the fact that a 100 per cent mortality followed this combination of agents. The inference that nembutal alone is deleterious because it produced a mortality of 50 per cent must be qualified in that the dose employed did not achieve complete anesthesia so that the relatively high mortality might have been due in part to an incomplete central suppression of the afferent impulses during the stimulus. The wide differences in mortality herein observed show how important it is to evaluate the effect of the anesthesia in experimental burns before drawing inferences from the value of various therapeutic procedures. In shock due to other injury contrasting findings have been reported. Thus, experiments<sup>2</sup> with hemorrhagic shock have shown no difference in mortality between those given morphine as compared with controls. Another study,<sup>3</sup> together with an analysis of preceding work, showed that shock from intestinal manipulation is delayed with barbiturate as compared with ether anesthesia, but that in shock from hemorrhage there was no significant difference.

Practical inferences may be drawn from the present study in view of the almost universal use of large doses of morphine in the treatment of human burns. While no one will question the beneficial effect of morphine in the presence of really severe pain, its cautious use must be emphasized when such pain does not exist. The present author has observed many severe human burns in which pain was completely absent at the time the patient was first seen. Indeed, the sensorium was often dulled in the severe cases. It is quite probable that by the time the burned patient is able to receive medical care, pain has disappeared almost entirely except for the memory of the intense pain at the very moment of the injury. Under such conditions, large doses of morphine should certainly not be used, inasmuch as it may lead to harmful effects, perhaps even increasing the mortality in spite of the use of other beneficial therapy.

#### CONCLUSIONS

Morphine increases the 24-hour mortality (up to 100 per cent) in severe experimental burns, particularly when given in large doses and with nembutal. Practically no 24-hour mortality occurred when ether alone was employed.

## ANESTHESIA IN BURNS

It is inferred that large doses of morphine, when used in the absence of pain, may increase the early mortality in severe human burns

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# CLOSURE OF DEFECTS OF LIPS WITH COMPOSITE VERMILION BORDER-LINED FLAPS\*

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DEFECTS OF THE LIPS large enough to prevent direct closure can be closed by transplantation of flaps either from the immediate neighborhood or from some distant parts. If possible, composite vermilion border-lined flaps shifted or rotated from the immediate neighborhood should be chosen. Flaps from distant parts have the disadvantage of requiring considerable amount of time for their transplantation, difference in skin color and texture, and loss of function.

## CLOSURE OF VERTICAL LIP DEFECTS NOT LARGER THAN HALF THE WIDTH OF THE LIP

**Estlander's Operation** The principle of the method consists in covering the defect by formation and rotation of a full-thickness flap from the opposing lip. The flap is pedicled at one side of the vermilion border, which contains the coronary artery. Estlander's original operation was devised for closure of triangular defects of the lower lip near the corner of the mouth. This operation has been modified, since then, in many ways (Abbé, Buck, Brown, Padgett, Cannon). Some of the different ways in which Estlander's principle can be employed are outlined in Figures 1, 2, 3, 4 and 9. In those defects in which the corner of the mouth is included, the pedicle of the flap forms the new corner of the mouth. This usually causes some vertical shortness and, consequently, prevents the patient from opening the mouth fully, Figures 1, 2, 3 and 9. To overcome the handicap, I recommend a procedure to be performed three weeks after the first operation, as outlined in Figure 2. The principle is based on the switching of triangular flaps like in Z operations. Thus, not only the oral orifice is widened, but a more natural corner of the mouth is achieved, Figures 2 and 9.

## CLOSURE OF LARGE HORIZONTAL DEFECTS OF UPPER OR LOWER LIP (EXCLUDING THE CHIN)

These defects may involve partial or full-length of the lips. A great number of procedures are described in the literature which recommend the use of full-thickness cheek flaps. Some of them have never been practiced and some of them give such poor cosmetic and functional results that they should be abandoned, both from surgical practice and textbooks.

Brun's operation is still highly recommended in some of the textbooks. This method was tried by the author, but was far from the result which the classic illustrations would make one believe. But, there are a few excellent procedures available which make use of flaps from the immediate

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\* Presented before the Philadelphia Academy of Surgery, December 1, 1943

# DEFECTS OF LIPS

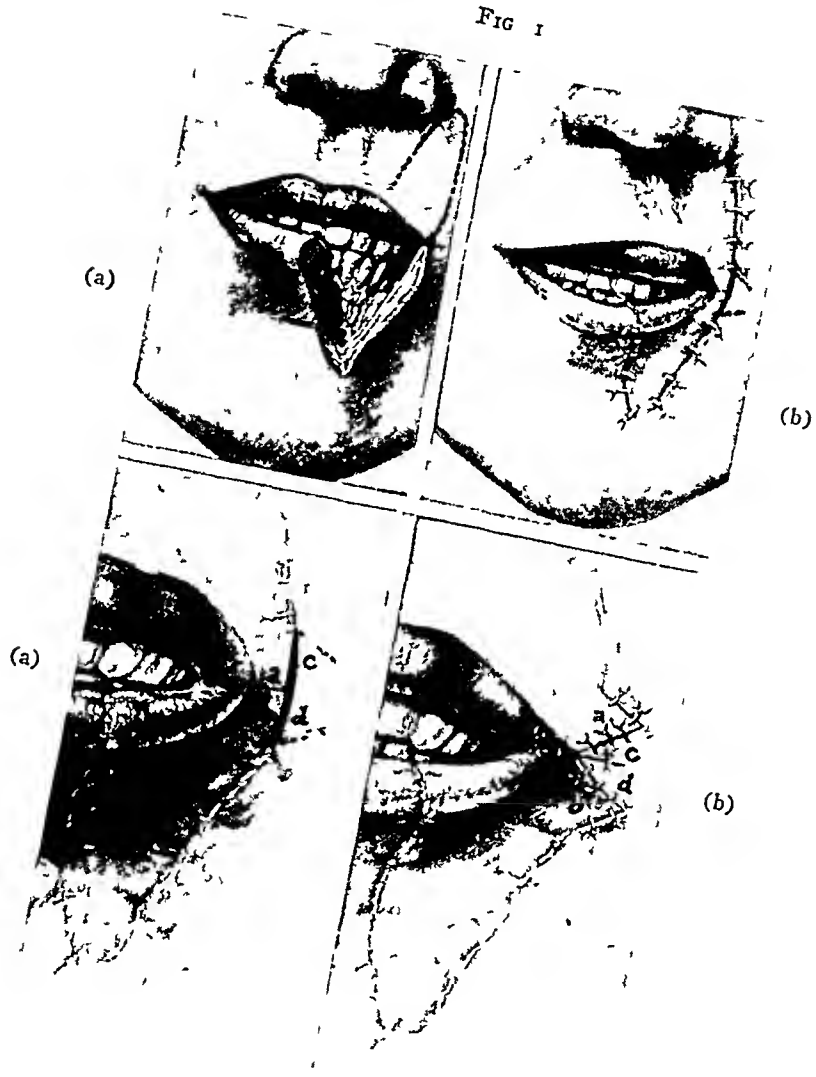


FIG 1

FIG 2

FIG 1—(a) Triangular defect of lower lip not larger than one half the width of the lip. The defect includes the lower border of the left corner of the mouth. To close the defect, a vermilion border lined flap is to be rotated from the upper lip and the nasolabial region. The pedicle of the flap containing the coronary artery is to replace the corner of the mouth. The flap should be made one half as wide as the defect in order to shorten upper and lower lip proportionately. (b) The flap is rotated into the defect. The secondary defect is closed by suturing the wound edges together.

FIG 2—(a) Reconstruction of corner of mouth in those cases in which the pedicle of the flap of mouth in 1) forms the new corner of the flap (see Figure 1). Flap (a) is overcome by switching triangular flaps. Flap (a) is exchanged with flap (c), flap (b) with flap (d). Thus not only the oral orifice is widened, but a more natural corner of the mouth achieved.



neighborhood consisting of skin and subcutaneous tissue only, and are recommended whenever they are possible. I refer to the ingenious methods of F. Smith, Pierce, O'Connor, and Owens.

#### CLOSURE OF DEFECTS OF LOWER LIP AND CHIN OF NOT LARGER THAN THREE-QUARTERS THE WIDTH OF THE LIP

For closure of these defects, utilization of composite flaps from the immediate neighborhood is still possible.

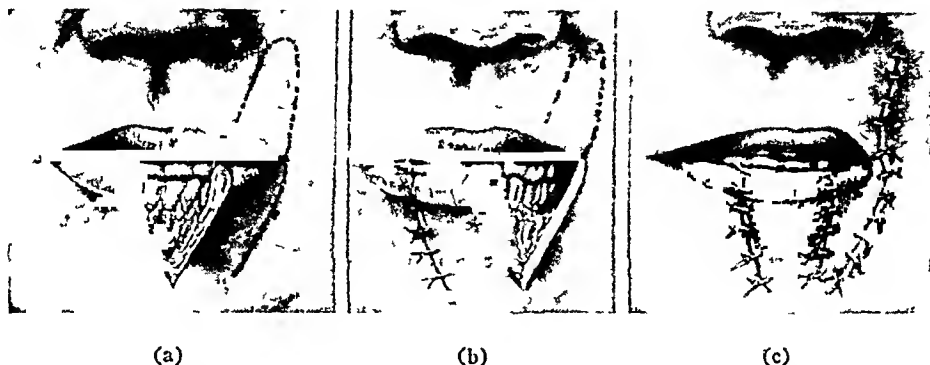


FIG. 3—(a) Triangular defect in the middle portion of the lower lip. In order to make the method of Figure 1 possible, the defect must be transferred laterally. This is done by closure of the center defect with a square flap. The outlines of this flap as well as the flap of the upper lip are illustrated. (b) The square flap for closure of the center defect is rotated into the defect. This opens up a similar defect in the lateral portion of the lip. (c) The flap from upper lip is rotated in the lateral defect. The secondary defect of the nasolabial region is closed.

**Burow's Method.** To use this method, the defect must be triangular-shaped. It is closed by shifting tissue from the immediate neighborhood into the defect after sacrificing two triangles of tissue in the nasolabial region.

The excision of lip and chin should be rather heart-shaped, than wedge-shaped (Diffenbach). This results later in a more normal looking profile with a dimple in the center of the chin.

The triangles of tissue to be excised from the nasolabial region should consist of skin and muscle only. The base of the triangle is in line with the vermilion border and equals in length one-half the width of the defect. The mucous membrane floor of the triangular defect is incised as outlined in Figure 5. If turned outward, it will lengthen the vermilion border. The purpose for shaping the small mucous membrane flaps, as outlined in Figure 5, is twofold: (1) A gradual tapering off of the new vermilion border at the outer angles which are to form the new corner of the mouth, and (2) a more satisfactory adjustment of the mucous membrane flap to the gradually disappearing original vermilion border. As a rule, a small triangle of skin needs to be removed at the corner of the mouth to make room for the tip of the mucous membrane flap (New and Figg). The flaps are now turned outward and sutured in place. The lateral part, however, where the new vermilion border is tapering off, due to thickness of the cheek tissue, may be too broad, it should be thinned somewhat by excision of a wedge of subcutaneous and muscle tissue.

## DEFECTS OF LIPS



FIG 4 — (a) Small recurrent cancer of left half of lower lip. Excision at lower lip and flap at upper lip marked out. The width of the flap is only one half of that of the defect, in order to shorten upper and lower lip proportionately. (b) After rotation of the flap, the left corner of the mouth is preserved, the pedicle of the flap crosses the mouth. (c) Three months after separation of the pedicle. (d) Mouth can be opened to almost full extent.

The cheek flaps to be shifted into the defect are mobilized from the mandible from an incision along the lower gingivobuccal sulcus. The dissection should be carried back to the anterior border of the masseter muscle. The mobilized flaps are now pulled forward and anchored in this position.

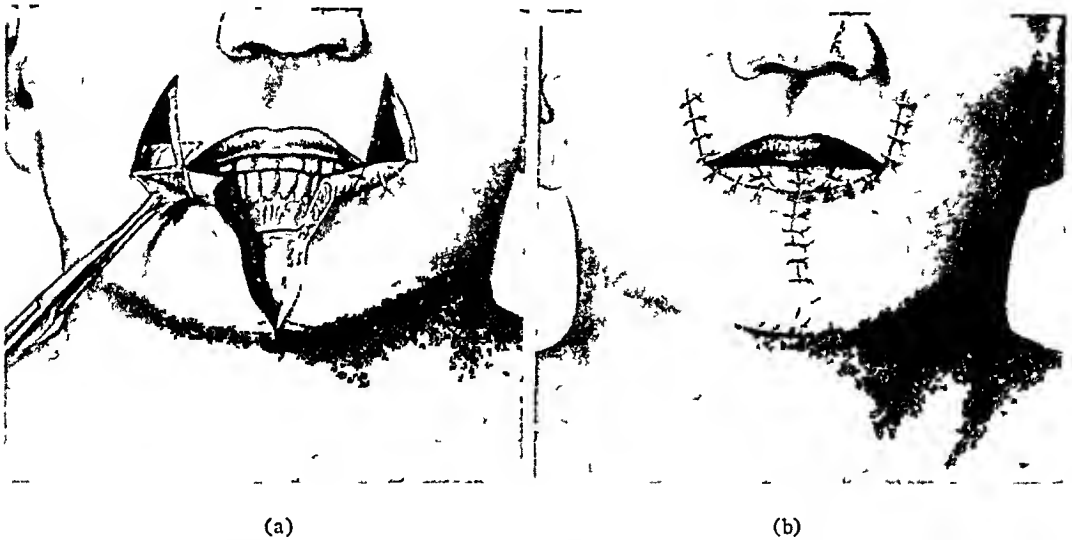


FIG 5—(a) Burrow's method of closure of triangular defects of lower lip and chin, of not larger than three quarters the width of the lip. Closure of the defect by shifting tissue from the immediate neighborhood into the defect after sacrificing two triangles of tissue in the nasolabial region. The excision of the triangles should consist of skin and muscle only. The incision of the mucous membrane floor of the triangular defect is outlined. If turned outward, the mucous membrane flaps lengthen the vermilion border. A small triangle of skin near the corner of the mouth needs to be removed for adjustment of the mucous membrane flap. A horizontal incision below the chin may facilitate shifting of the main flaps. (For details, see text.) (b) After closure of primary and secondary defects.

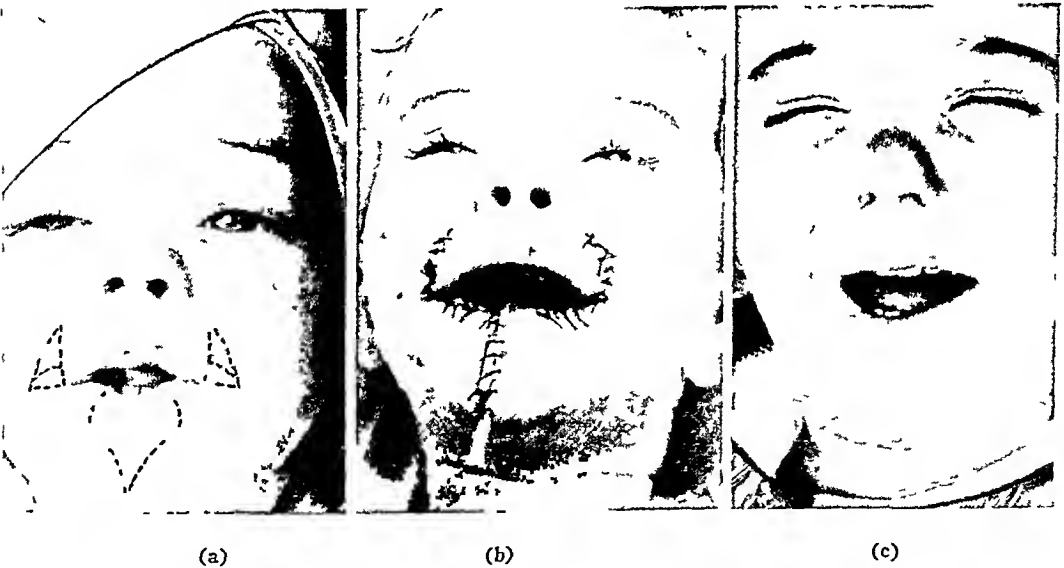


FIG 6—(a) Defect of lower lip and replacement of soft tissue by dense fibrous tissue after radiation of a hemangioma. Patient was operated upon according to the method of Figure 5. (b) Soon after the operation. (c) One year after the operation.

to the gums. Each suture should be placed obliquely so that it advances the flap forward. Then follows closure of the triangles in layers, connection of the lateral edge of the new vermilion border to the upper lip and vertical connection of both flaps in the midline in layers. Some adjustment may be

necessary at the bottom of the incision to avoid pointing of the chin. A drain is inserted in the lower corner of the vertical wound.

**Variations** If the defect is more laterally situated this method may be

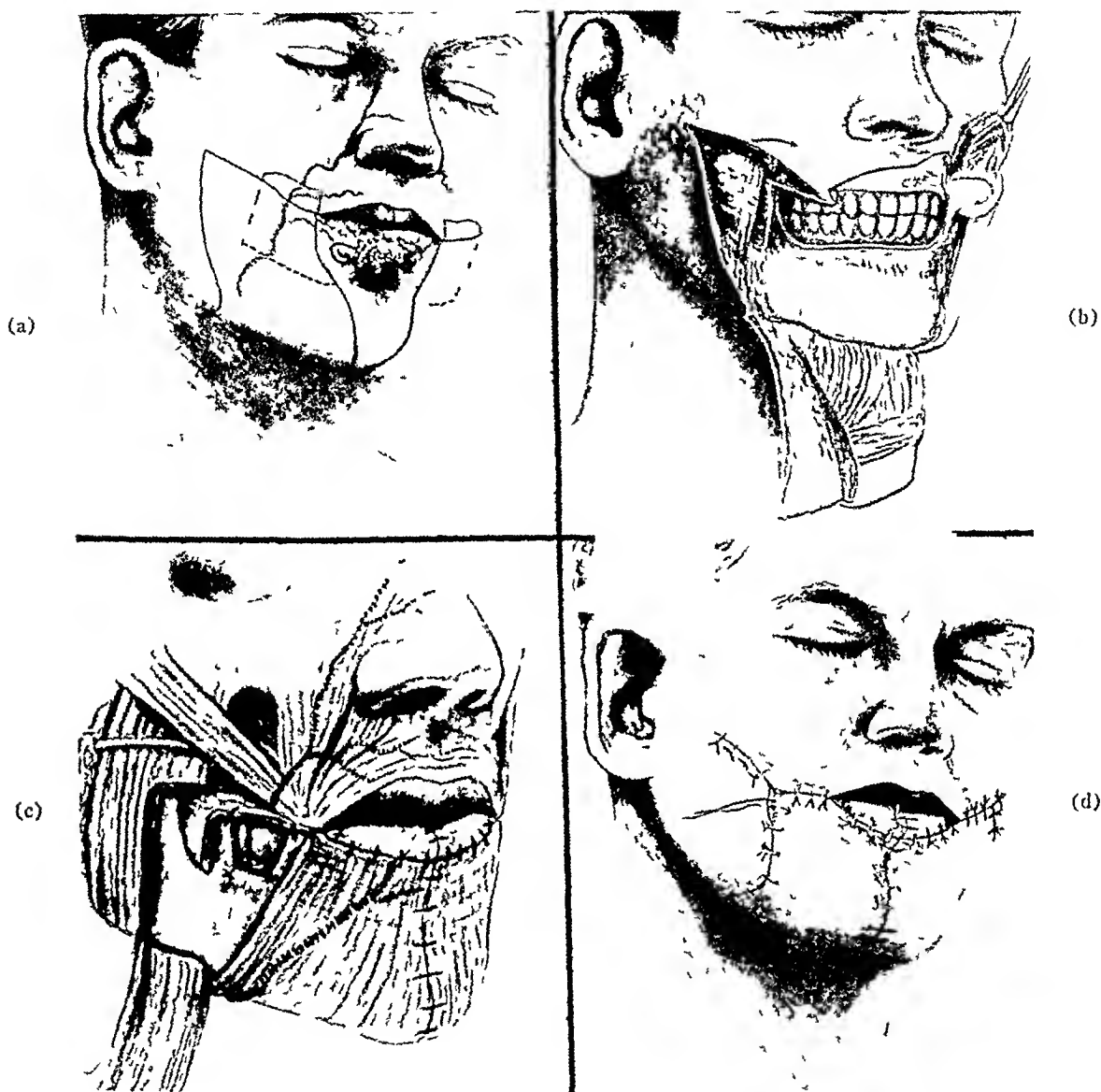


FIG 7—(a) Modified Dieffenbach's method for closure of large defects of lower lip and chin. Heart shaped excision of lower lip and chin is outlined, also the two square flaps which are to cover the defect. Two small flaps at corner of mouth are preserved, the inside incisions for mobilization of the flaps from the mandible and from the anterior border of the masseter muscles are outlined by dotted lines, also the small mucous membrane flaps for formation of the vermillion border. (b) The right flap is mobilized, the small mucous membrane flap is sutured to the outer edges of the main flap, the left mucous membrane flap for formation of the vermillion border is being freed. (c) Closure of the triangular muscle and mucous membrane defect in front of the masseter muscle by mobilization of the mucous membrane as far as possible and transplantation of a flap consisting of the lower anterior half of the masseter muscle. The mobilization of the flap is exaggerated in this drawing for demonstration purposes. (d) The original and secondary defects are closed. (Courtesy, Surg Gynec & Obst 73: 236, 1941.)

carried out unilaterally and be combined on the other side either with Estlander's or—in large defects—with Dieffenbach's method (*vide infra*).

**Bernard's Operation** This operation is similar to Burow's, with the exception that the defect is made square, instead of triangular. Martin improved the technic by adding some modifications.

## CLOSURE OF DEFECTS OF ENTIRE LOWER LIP AND CHIN

In such large defects, a lined flap from distant parts of the body will be the method of choice in a number of cases, particularly for square, irregularly-shaped defects. If, however, the defect can be made triangular, transplantation



FIG 8—(a) Patient with large squamous cell carcinoma of lower lip—no evidence of metastasis. Line of heart shaped excision outlined. Operation according to the method of Figure 7. (b) Same patient five days after operation. (c) Same patient 13 months after operation. (d) Same patient 13 months after operation. (Courtesy, Surg Gynec & Obst 73: 236, 1941)

of composite flaps from the immediate neighborhood may be possible. I recommend the modified Dieffenbach operation for such a case. This method has been frequently accused of being mutilating and extensive. It will not be denied that the operation is extensive, but—correctly performed—it is not mutilating. I have endeavored to improve the technic by adding a few more modifications. From the cosmetic functional and economic standpoint, it is by far superior to any existent flap transplantation. The advantages are: Excision

sion of the diseased part and closure of the defect in one sitting, thus shortening hospitalization, and replacement of lost structures by similar structures, thus restoring original function and appearance. This operation can be performed unilaterally or bilaterally, it can be combined with other operations such as Estlander's or Burow's, it can also be combined with resection of



FIG 9—(a) Patient with squamous cell cancer inside the mouth near right corner. Triangular excision including upper half of corner of mouth and parts of the adjacent cheeks is outlined. Triangular vermilion bordered flap at lower lip is outlined. (b) Before the flap was rotated into the defect, the latter was made smaller by closure of the lateral corner. The pedicle of the flap forms the new corner of the mouth. (c) Four weeks after operation. (d) The vertical shortness at the right side of mouth was corrected according to the method of Figure 2.

bone. I have described the technic in a previous publication. Figures 7 and 8 depict technic and result. Lymph-glands, if necessary, should be resected in a second stage.

#### CLOSURE OF DEFECTS OF THE CORNER OF THE MOUTH AND PARTS OF THE ADJACENT CHEEK

If the defect includes only one-half of the corner of the mouth (the corner part of either the upper or lower lip), and parts of the adjacent cheek, and

if the defect can be made triangular, Estlander's method is the operation of choice. The patient in Figure 9 is a typical example. Before rotating the vermilion-bordered triangular flap into the defect, the latter is made smaller by starting with closure of the lateral corner of the triangle until the corner of the mouth, *i e*, the remaining half of it, is reached. Now, the triangular flap is formed from the sound lip opposite to the defect and rotated into the defect as described above. In a second stage, the pedicle of the flap

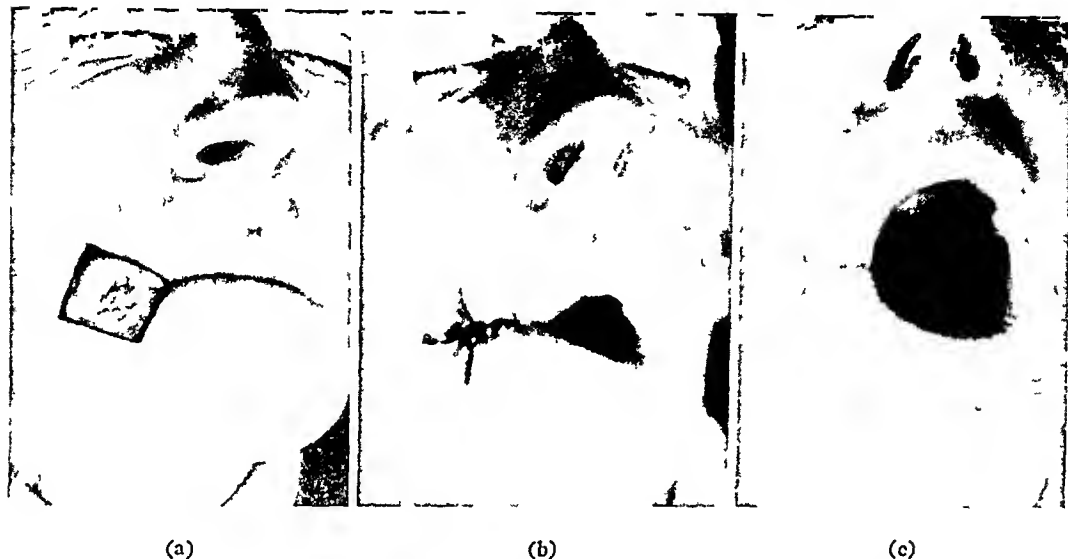


FIG 10—(a) Patient with long standing keratosis cancer in right corner of mouth. Diamond shaped excision outlined. (b) After closure of the defect by starting with closure of the corners. (c) Same patient six months after first operation and five months after correction of shortness of right side of mouth according to the method of Figure 2.

is severed and adjusted as shown in Figure 2. This will widen the oral orifice and achieve a more natural corner of the mouth.

If the upper and lower part of the commissure, *i e*, the entire angle of the mouth and adjacent parts of the cheek, must be excised, and the resulting defect is of such size that closure can be achieved by simple skin sliding, the defect should be given a shape, as outlined in Figure 10. An upper and a lower triangle with a common base, resulting in a diamond-shaped defect. The latter is closed by starting with closure of the corners, Fig 10. If this procedure results in a microstoma on the operated side, the deformity can be improved according to the method of Figure 2.

#### SUMMARY

Various operations to close defects of lips alone, or lips, chin and cheek, with composite vermilion border-lined flaps from the neighborhood, have been described. Only those methods have been selected which have proven to be of practical value.

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# DUPUYTREN'S CONTRACTURE FIBROMA OF THE PALMAR FASCIA

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THE PROGRESSIVE unilateral or bilateral contracture of the fingers of the ulnar side of the hand, which we know as Dupuytren's contracture, had been described prior to 1832, when the great French surgeon whose name it bears called attention to the fact that the actual shortening occurred in the palmar fascia and did not involve the tendons. This observation has since been universally confirmed and, on this basis, successful surgical treatment has been possible. Despite numerous subsequent attempts to explain the nature of the change in the palmar fascia, no satisfactory theory of etiology has as yet been advanced. It is the purpose of this paper to show that Dupuytren's contracture is due, in a series of cases, to a neoplasm—a cellular fibroma of the palmar fascia.

## THEORIES OF ETIOLOGY

Some of the many theories of the nature of Dupuytren's contracture may be mentioned, though many have not received adequate support to warrant discussion here. Abbott,<sup>1</sup> quoting from many sources, mentions the possible contributions of a familial trait, an ulnar nerve lesion, endocrine disturbances, and dental and tonsillar sepsis. There can be no controversy over the fact, repeatedly observed by many writers, that several persons in the same family and in succeeding generations may suffer from the contracture, but this interesting fact actually casts no light on the cause or nature of the disease. The suggestion that there may be a lesion of the ulnar nerve seems to grow out of the predilection of the contracture for the ulnar side of the hand, though rarely, if ever, can such a lesion be demonstrated. The frequent simultaneous occurrence of Dupuytren's contracture and arthritis, together with the difficulty of adequately explaining the cause of either, has led to the suggestion that focal infection, thought by many to be implicated in arthritis, might play a rôle in the contracture as well.

Kanavel, Koch, and Mason<sup>2</sup> have gathered from the literature five additional suggested causes. These are trauma (Dupuytren himself thought the disease resulted from repeated trauma), local inflammation, lead poisoning, loss of fat with advancing age, and embryonic malformation. They discuss the rôles of trauma, "a constitutional vice like gout or rheumatism," and heredity. In eight out of 29 patients they elicited a definite family history of Dupuytren's contracture. They found that their patients had

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about the same incidence of gout and rheumatism as could be found in a group of comparable ages, not suffering from contracture. Sixteen of their patients gave histories of trauma to the palm to which they attributed their disease. The authors point out that the histories are all unconvincing. They ultimately conclude that the etiology of the contracture is unknown.

Gill,<sup>3</sup> and Davis and Finesilver<sup>4</sup> point out the unlikelihood of trauma as an etiologic agent because (a) the disease usually has a late onset after the completion of the working years, in which trauma to the palms is most likely to be sustained, (b) there are relatively few cases among laborers and many among "white-collar workers" (Kanavel, Koch, and Mason reported 321 cases of which 175 occurred in nonlaborers, while 146 were in laborers), (c) trauma is usually unilateral, while the contracture is often bilateral (313 cases out of 648 reported by Kanavel, Koch, and Mason), and (d) trauma to the palm is much more common than Dupuytren's contracture.

Brooks<sup>5</sup> has reported a case in which a unilateral Dupuytren's contracture was associated with an aneurysm of the axillary artery, and which almost entirely disappeared following proximal ligation and distal reconstructive endo-aneurysmorrhaphy of the aneurysm.<sup>6</sup> In this connection, the author recalled as examples of fibrosis associated with impairment of blood supply the contracture of Volkmann, and the scarring of the tissues of the leg distal to varicose veins.

The suggestion that the contracture is due to a neoplasm is rare in the literature. Horak,<sup>7</sup> histologically, found no actual inflammation, and concluded that the process lay on the borderline between inflammation and new growth. McWilliams<sup>8</sup> stated that the process was a "chronic hyperplastic inflammation of the palmar fascia and adjacent connective and fatty tissue" involving only certain portions of the tissue at a time and producing the "small tumors felt in the palm."

Ewing,<sup>9</sup> though he states that the etiology of the contracture is undetermined and does not actually say that it is a neoplasm, implies a recognition of its neoplastic character by discussing it in the chapter on fibromata in his book, "Neoplastic Diseases." The issue is somewhat clouded, however, by the unfortunate fact that the condition is classified under tumors of peripheral nerves in the subgroup "elephantiasis," which also includes inflammatory types. He states "Hyaline changes are not infrequent and the structure then resembles that of keloid. Occasionally, the structure is more cellular and resembles hyaline neurofibroma, with appearance of somewhat numerous, large polyhedral cells of uncertain origin." Unfortunately, the vagueness of these statements makes it difficult to be sure whether Ewing believed the contracture was neoplastic.

In this connection it is of interest that McWilliams,<sup>8</sup> Kanavel, Koch, and Mason,<sup>2</sup> Abbott,<sup>1</sup> Meyerding,<sup>10</sup> and Davis and Finesilver,<sup>4</sup> all emphasize the fact that the first symptom of contracture is a palpable nodule in the palm.

The material for this study comes from 22 hands of 17 patients operated upon for Dupuytren's contracture in the Johns Hopkins Hospital, and from

whom excised tissue was saved for study Fifteen cases were in males and two cases in females The contracture was unilateral in 10 cases and bilateral in seven, but one hand of one patient had previously been operated upon elsewhere, and the specimen from one hand of another is no longer available In 15 patients the history of onset is available and in eight of these a nodule in the palm was the first thing noticed, even before contracture began Five patients stated that other members of their families suffered from contractures of the fingers In only one case was there a history of trauma to the palm, while in three this factor was not touched upon in the history

The histologic picture of the tissue excised is surprisingly uniform In 17 hands of 14 patients there are areas of rather cellular fibroma interspersed with areas of hyaline-appearing fascia Among the five cases with bilaterally operated contractures, from both of whose hands tissue is available, tumor is

TABLE I  
FINDINGS IN SEVENTEEN CASES OF DUPUYTREN'S CONTRACTURE

Case No	Unit No	Sex	Hands Involved	History of Trauma	Family History	Onset with Nodule	Fibroma Found
1	227601	M	1	0	+	0	+
2	195763	M	1	0	0	0	+
3	187206	M	1	0	0	+	+
4	170333	F	1	0	+	+	+
5	135119	M	1	0	0	0	0
6	57522	M	1	?	0	?	Skin only
7	52836	M	2				+
			1 lost	0	+	+	0
							Subcutaneous tissue only
8	44676	M	1	0	0	+	+
9	36027	M	1	?	0	+	+
10	35603	M	1	?	0	?	+
11	25406	M	2				
			1 operated	0	0	0	+
12	146873	F	1	0	0	+	+
						0	+
13	262778	M	2	0	+	0	+
						0	0
14	30531	M	2	0	0	0	+
						0	0
15	61976	M	2	+	0	0	0
						+	+
16	38855	M	2	0	0	+	+
						+	+
17	283453	M	2	0	+	+	+
Totals		15 male 2 female	22	1	5	8 cases 10 hands	14 cases 17 hands

present bilaterally in three cases, absent bilaterally in one case, and present unilaterally in one Of the 17 hands which histologically show fibroma, three failed to do so in the original section, and the neoplasm was revealed only on serial section of the blocks of tissue saved Serial sections were also made from the blocks of the five hands which failed to reveal fibroma, and one of these proved to consist only of skin and subcutaneous tissue, while another was subcutaneous fat only—indicating that in these cases either the operator or the pathologist missed the palmar fascia The other three negative blocks

show hyaline-appearing fascia identical with that which is interspersed between the areas of tumor in the remaining cases. Since in each case the pathologist imbedded for sectioning only a representative piece of the tissue removed, and since in three cases mentioned above only hyaline fascia was seen until the blocks were sectioned serially, it is possible or even probable that fibroma was actually present in the negative cases also. These data are recorded in Table I.

#### HISTOLOGY OF TUMORS

The fibromata in these cases are rather poorly demarcated, fading out into the surrounding fascia. They are composed of small, spindle-shaped cells, with elongated nuclei which contain finely granular chromatin particles. The cytoplasm is scanty and poorly outlined. These cells are imbedded in a matrix of fibrous tissue whose wavy pattern is suggestive of normal fascia or tendon. There are suggestions of whorls, and the bundles of cells run in various directions, some lying in the plane of, and some perpendicular to, the plane of any section. No mitoses are seen, and the cells are all quite alike. Inflammatory cells are so rare as to be almost nonexistent. Photomicrographs of representative cases of these tumors, demonstrating these various characteristics, are seen in Figures 1-3, inclusive, while a higher magnification, to indicate the waviness of the stroma, is seen in Figure 4.

These fibromata are histologically almost identical with the benign fascial fibromata seen elsewhere, especially with desmoid tumors of the abdominal wall. Two of these latter tumors are shown in Figures 5 and 6, for comparison. Figure 7 shows another histologically similar fibroma which arose from the fascia of the popliteal space, and Figure 8 is another such tumor which originated in the plantar fascia of the foot. These latter tumors, while they slowly invade the surrounding structures, do not metastasize. Quite obviously, the benignancy of the fibroma seen in Dupuytren's contracture is confirmed by the failure of the literature to record metastasis in any of the many reported cases.

#### CONCLUSIONS

No real conclusion as to the etiology of Dupuytren's contracture has previously been reached. In general, various suggestions have been made—trauma, familial trait, focal infection, ulnar nerve lesions, endocrinopathy, local inflammation, embryonal malformation, palmar atrophy with advancing age, and lead poisoning, *etc*. None has been generally accepted, and much of the discussion of etiology has been directed toward proving that these are *not* the causes of the contracture.

While to say that a lesion is a neoplasm is admittedly no explanation of its cause, it at least indicates the general type of abnormality with which one has to deal. The present study of tissue removed from 22 hands of 17 patients with Dupuytren's contracture reveals areas of cellular fibroma in the palmar fascia in 17 hands of 14 patients, while the tissue from two hands does not

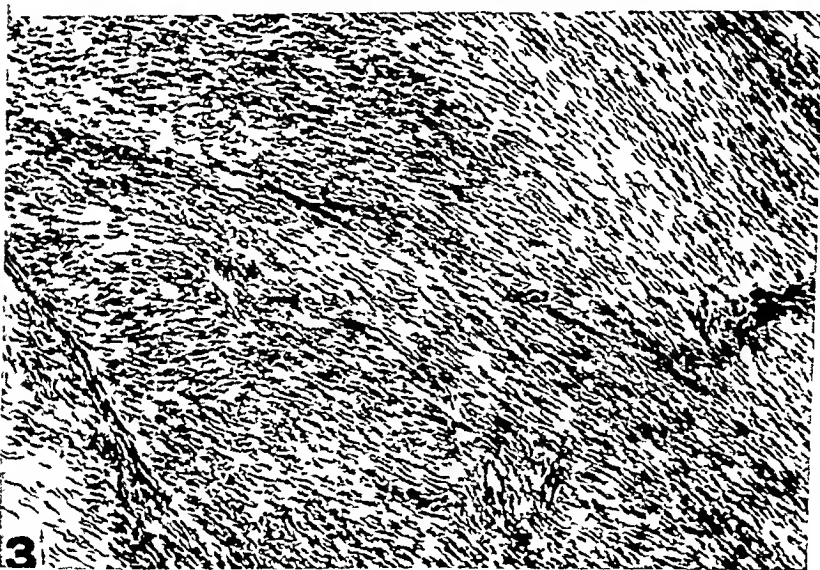
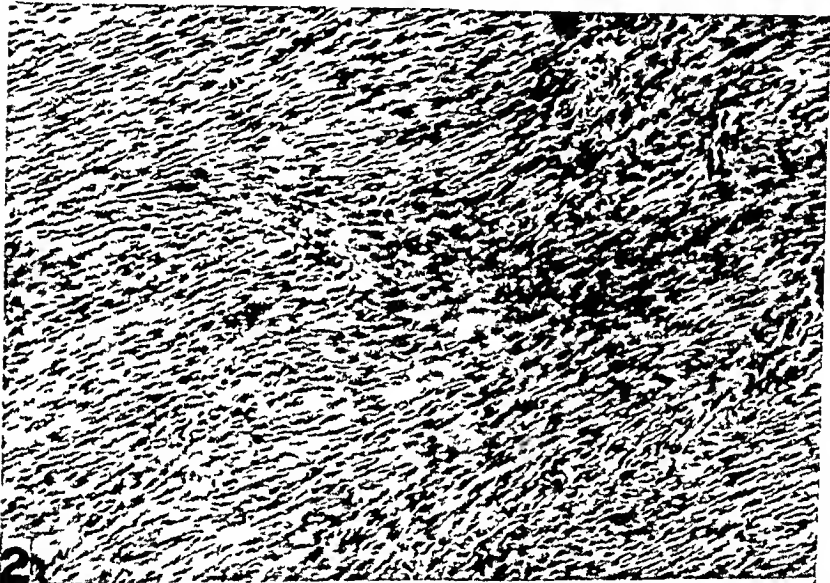
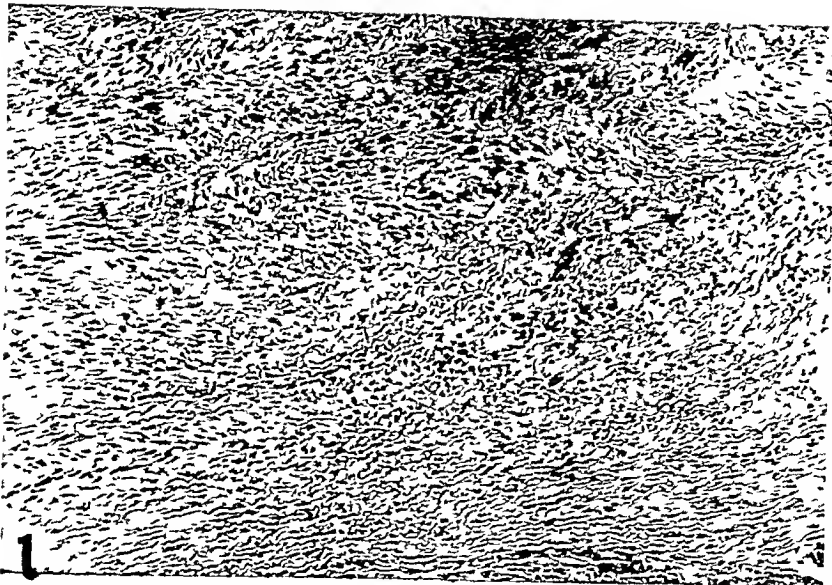


FIG. 1.—Case 1. Fibroma of palmar fascia from Dupuytren's contracture. Tumor is composed of elongated cells in a fibrous matrix. Bundles of fibers and cell nuclei course through tumor in various directions.  
 FIG. 2.—Case 11. Fibroma of palmar fascia from Dupuytren's contracture.  
 FIG. 3.—Case 17. Fibroma of palmar fascia from Dupuytren's contracture.

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- FIG 4—High power magnification of fibroma of palmar fascia from Case 11, showing wavy fibrillary pattern of stroma
- FIG 5—Fibroma of fascia of abdominal wall (desmoid tumor) from a 25 year-old white male (Compare with Figures 1-3)
- FIG 6—Fibroma of fascia of abdominal wall (desmoid tumor) from a 24 year-old white female (Compare with Figures 1-3)



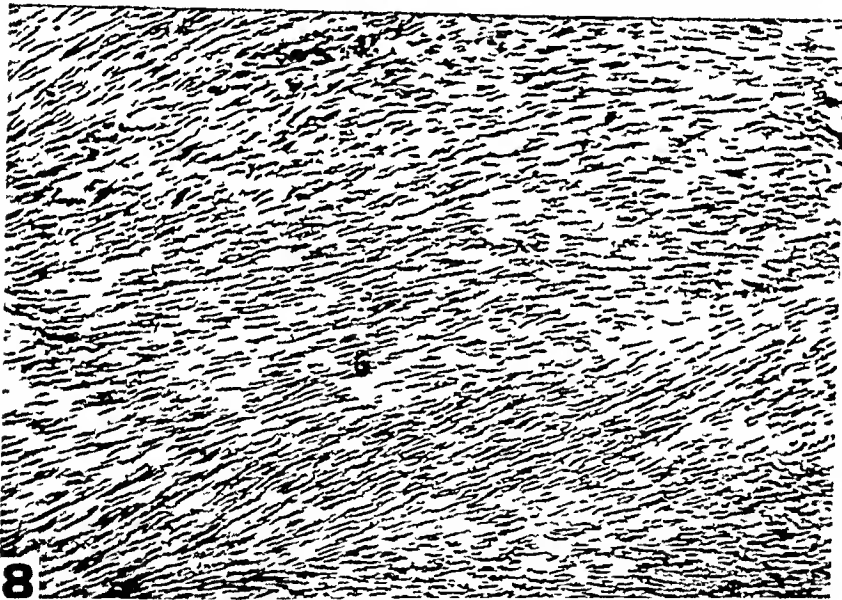
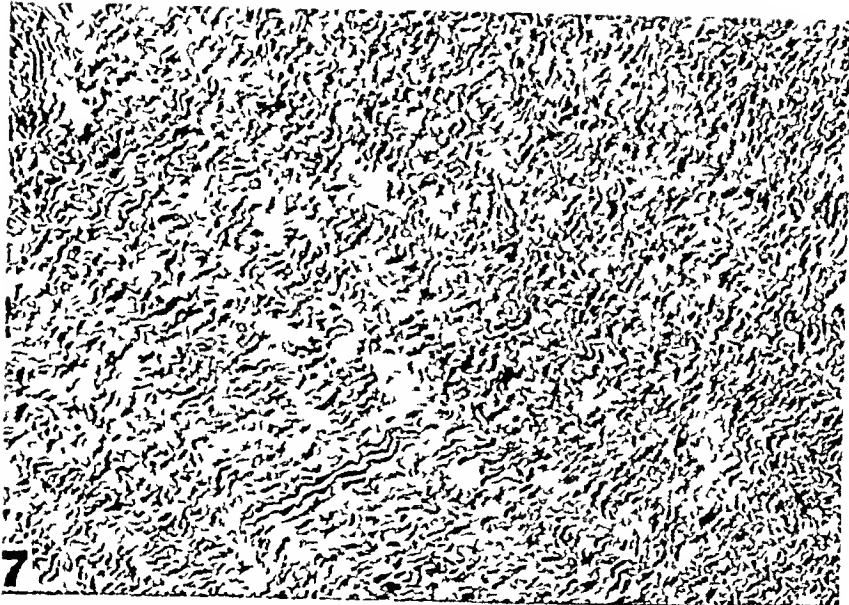


FIG 7—Fibroma of fascia of popliteal space from a 23 year old white female  
(Compare with Figures 13)

FIG 8—Fibroma arising in plantar fascia of a 21 year old white female  
This tumor had been present since childhood and was 2 cm in diameter  
(Compare with Figures 13)

include the palmar fascia. As has been pointed out, the method employed in preparing the specimens for microscopic examination makes it possible that tumor was present in the palmar fascia of the three remaining hands.

In addition, in eight of the 15 patients in whom a history of onset is available, a palpable nodule in the palm was the first symptom of the disease, even preceding the onset of contraction of the fingers. This is in agreement with the histories, previously quoted by several authors, and seems very significant in the light of the subsequent histologic finding of fibromata.

The predominance of males, 15 of 17 patients, as well as the family history

## DUPUYTREN'S CONTRACTURE

of Dupuytren's contracture given by five patients, agrees with previously reported data. It would be of interest to see whether other fascial fibromata, including the desmoid tumors, have a tendency to familial occurrence. This point has generally not been mentioned in the recorded cases, and in one large series<sup>11, 12</sup> it was not observed. Among 14 patients whose history touches on this point, only one gave any suggestive history of trauma to the palm.

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# OMENTAL CIRCULATION IN MORPHINIZED DOGS SUBJECTED TO GRADED HEMORRHAGE\*

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THE CAPILLARY BED, as an organized, functioning unit, offers the logical site for a study of shock involving a progressive deterioration and an ultimate failure of the peripheral circulation. Recently Root and Mann,<sup>1</sup> and Page and Abell,<sup>2</sup> studied this aspect of the problem by making direct observations on the peripheral circulation in the mesentery of experimentally treated animals. Root and Mann subjected rats to tourniquet shock and reported a general congestion of the capillaries which they concluded was not to be ascribed to histamine. Page and Abell studied the effects of hemorrhage and of venous tourniquets on cats and dogs. They reported an over-all ischemia of the capillary bed resulting from a widespread vasoconstriction.

Unfortunately, in the above investigations, no special attention was given to several important points. One of these deals with the independent reactions of the capillary bed, a feature stressed by those who have made a specialty of the capillary circulation, (Lewis,<sup>3</sup> Krogh,<sup>4</sup> Dale and Richards,<sup>5</sup> and, more recently, Zweifach<sup>6</sup>). A second point is the danger of generalizing from one set of observations without ascertaining the extent to which the vascular bed studied is typical. A third point, which is probably the most important and applies particularly to the observations of Root and Mann, is the necessity of rigid precautionary measures for obviating trauma incidental to handling of a tissue while preparing it for the observations. Krogh,<sup>4</sup> Landis,<sup>7</sup> and others, have emphasized that even slight abnormalities of the surroundings seriously affect the behavior of the capillary vessels. This is especially true for mammalian tissues where not only a minimum of handling, but also anesthesia, temperature and the make-up of the bathing medium play a crucial rôle. The significance of the normal reactivities of the capillary circulation

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in the dog and rat and the means for maintaining them have been presented in detail elsewhere<sup>8, 13</sup>

It is well established that various types of trauma involving fluid loss are accompanied by a widespread vasoconstriction. Investigators who have examined the peripheral circulation in the cutaneous tissues<sup>9, 10, 11</sup> where little or no handling of the tissue was involved in making the observations, agree on the development of a marked vasoconstriction resulting in complete ischemia of the tissue. Page and Abell<sup>2</sup> claim this to be true also for the intestinal mesentery exteriorized in a specially constructed transparent chamber. In an earlier publication from our laboratory,<sup>12</sup> observations were made simultaneously on the cutaneous vessels of the interdigital web and the visceral vessels of the meso-appendix of rats traumatized by the Noble-Collip drum. It was found that the vasoconstriction affected the cutaneous much earlier than the visceral vessels. Moreover, the ischemia of the skin vessels was so complete as to render visualization of the capillary bed very difficult even during the earlier stages of the shock syndrome. On the other hand, the visceral vessels remained plainly visible throughout the syndrome and the progressive changes in the capillary bed could be readily followed.

An analysis of the structural and functional aspects of the normal peripheral circulation in the frog and mouse has been presented by Zweifach.<sup>13</sup> This has been more recently amplified by a study of the normal visceral capillary circulation in animals which are commonly used for shock studies, *viz*, the rat and the dog. On the basis of the findings on the meso-appendix of the rat and the omentum of the dog, a number of well-defined criteria have been assembled which make it possible to analyze, more adequately than hitherto, changes which are induced by various experimental procedures.

This paper is restricted to a study of the circulatory changes in the omentum of morphinized dogs induced by a specific type of graded hemorrhage<sup>14, 15, 17</sup>. Hemorrhage as a procedure for inducing shock was selected because it offered a relatively simple and controllable approach to the problem. A study of circulatory collapse induced by acute hemorrhage is being presented in another paper.<sup>16</sup> This study deals more particularly with the effect of inducing hypotension in morphinized dogs and of prolonging the hypotension (by repeated small infusions) until a circulatory collapse occurs which is refractory to the infusion of all the blood withdrawn during the syndrome.

#### TECHNIC

*Preparation of the Omentum*—The dogs were given a subcutaneous injection of morphine sulfate (12 mg/Kg) and, 30 to 45 minutes later, part of the omentum was carefully withdrawn through a transverse abdominal incision and was spread on a specially constructed moist chamber on the stage of a microscope. This method, the details of which are given in a previous paper, maintains the exposed omentum with a normal circulation for six to eight hours. The essential feature is maintenance of the entire

exposed portion at body temperature and moistened with a constant drip of warm gelatin-Ringer's solution\*. The observations were made on selected vessels throughout the course of an experiment, under magnifications of 80 to 345 times

*Bleeding*—The method of bringing the dogs into a hypotensive state, from which they no longer can be restored by the infusion of the blood withdrawn, is essentially that recommended by Wiggers and Werle<sup>17</sup>. The dogs were routinely bled at 10- to 15-minute intervals by the successive removal of blood in amounts of 20, 10, 0.5 and 0.25 percentages of the body weight, or until the blood pressure reached hypotensive levels below 70 Mm. The pressure was taken from the carotid, and a continuous record made on a kymograph drum throughout the experiment. The dogs were first brought to, and kept in, moderate hypotension, within the range of 50 to 70 Mm. Hg, for varying lengths of time, and then were brought into diastolic hypotension and kept there for another length of time. The blood withdrawn was preserved with 0.2 per cent sodium citrate for infusion purposes.

The majority of the dogs (46 out of 65) could not be kept at the drastic hypotensive levels (below 45 Mm. Hg) for more than 1 to 1.5 hours without showing signs of sudden collapse. The remaining 19 were more resistant and, after 1.5 hours of drastic hypotension, were further bled cautiously until their blood pressure showed a similar tendency to fall precipitously. All the dogs were then sustained by small blood infusions (2-3 cc./Kg.) for an additional 30 to 90 minutes. By this means, it was possible to keep dogs in a state which they otherwise could not maintain over a protracted period.

*Restoration of Blood Volume*—At the end of a given period of drastic hypotension the dogs were infused with the remainder of the blood which had been withdrawn during the hemorrhage. Dogs were considered to be irreversible if the infusion resulted in a blood pressure rise which was unsustained and which was followed by a drop to shock levels of hypotension within one to two hours. Dogs were considered to be reversible if their blood pressure rose to, and was sustained at, normal levels for at least two to three hours.

#### CRITERIA FOR DETERMINING THE STATE OF THE OMENTAL CIRCULATION

The determination of these criteria requires an understanding of the architecture of the capillary bed. Data concerning this appear in our previous publication<sup>8</sup>. In brief, the capillary bed is to be regarded as an interrelated series of specifically functional units, each unit consisting of a central channel leading from arteriole to venule and communicating, by means of side-branches, with the true capillaries. Figure 1 is a diagrammatic sketch of such a unit in a portion of the capillary bed in the omentum together with the nomenclature and characteristics of the various structures.

\* The solution had the following constitution in grams per cent in water: Granular gelatin, 1, NaCl, 0.8, KCl, 0.02, CaCl<sub>2</sub>, 0.02 and NaHCO<sub>3</sub> sufficient to bring the solution to pH 7.2-7.4.

The factors which condition the distribution of blood in the capillary bed act chiefly on the muscular vessels proximal to the capillaries, *e g*, the arterioles, metarterioles and precapillaries. Listed below are several criteria associated with these vessels and with the capillaries and muscular venules.

*Caliber of Arterioles and Muscular Venules*—Consecutive changes in caliber were always observed on the same vessels and were routinely determined under magnifications of 150 to 210 x by comparing them with the diameter of the red cells. In some cases, the diameters were measured directly by means of an ocular micrometer.

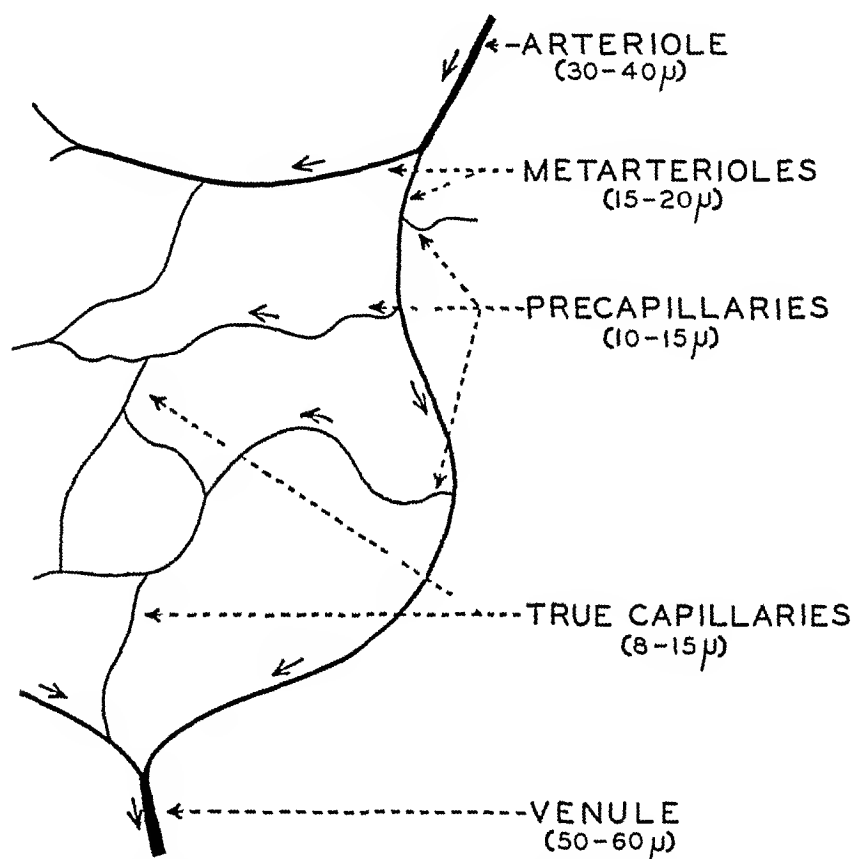


FIG. 1—Line drawing of a portion of the capillary bed in dog's omentum in which is given the nomenclature used for the different vascular components

*Threshold Constrictor Response to Epinephrine*—This was obtained by applying to the surface of the omentum, three to four drops of epinephrine in gelatin-Ringer's solution. A determination was made of the minimal concentration which temporarily produced a narrowing of a selected metarteriole sufficient to interrupt the blood flow into its precapillary offshoots for not longer than one to two minutes. This was regarded as a threshold response and similar tests were made at intervals throughout the experiment. The omental surface was always thoroughly irrigated between successive tests, which were spaced at least two to three minutes apart. A concentration of epinephrine in gelatin-Ringer's solution of 1.6 to 8 million, on the average, was found to be the normal threshold value for unbled, morphinized dogs.

*Vasomotion*—The metarterioles and precapillaries show a characteristic periodicity of alternating dilatations (dilator phase) and contractions (constrictor phase) at intervals of about 20 seconds to three or more minutes. Records were made of several metarterioles and precapillaries before starting the bleedings, and these vessels were kept under observation throughout the experiment. The vasomotion was designated as *augmented* when the rate in periodicity of the dilator and constrictor phases was accelerated and when the duration of the constrictor phase was increased over that of the dilator phase. The vasomotion was designated as *diminished* when the frequency of the periodic movements was reduced and when the duration of the dilator phase became progressively longer than that of the constrictor phase.

*Capillary and Venular Flow*—The rate of flow through the true capillaries and venules was noted throughout. Under normal conditions, this flow is so rapid that the individual blood corpuscles cannot be distinguished. The term "*slowed*" is applied to the condition in which the blood cells could be individually distinguished. The term "*sluggish*" is applied when the flow was slowed to such an extent that the blood cells become crowded together. The term "*stagnant*" indicates an almost complete cessation of flow.

*Pooling and Trapping*—This indicates an accumulation of blood in regions of the capillary bed which are being by-passed by an active circulation elsewhere in the bed.

#### EXPERIMENTAL

The dogs were subjected to graded hemorrhage after having been given morphine, and their omenta exposed for microscopic observation. In the earlier experiments, dependence was placed chiefly on the hypotensive levels attained and on their duration. The desired length of the hypotensive period was generally determined by small test infusions. Later, with increasing knowledge of the progressive deviation from the normal condition of the omental circulation, it was found possible to use these as criteria with which to determine the stage when the dog no longer could be brought back to a sustained level of its normal blood pressure by whole blood infusions. The establishment of these criteria is one of the chief purposes of the experiments described in this paper.

Many dogs with a blood pressure of 50 Mm were found to be in better condition and showed better capillary flow than others with a pressure of 80–85 Mm. Moderate hypotension was determined to be that state in which the capillary flow became significantly slowed with no marked change in the outflow by way of the venules. Drastic hypotension was ascertained by the additional development of a sluggish outflow by way of the venules.

The dogs were classified into three general groups on the basis of differences in their ability to tolerate the blood loss. This is shown in Table I, in which the percentage of blood loss and the duration of the moderate and drastic hypotensive levels are given for each group. When, at

the end of the experiments, the original blood volume was restored, 11 dogs showed a sustained rise of their blood pressure and a complete recovery of their omental circulation for two to three hours after the infusion. The remaining 54 did not respond and died within one to two hours after the infusion.

TABLE I  
REACTIONS OF DOGS TO SPECIFIED TYPES OF GRADED HEMORRHAGE

	Resistant Group	Typical Group	Unstable Group	Total No of Dogs
Blood-loss by per cent of body weight	4 0-4 5%	3 0-4 0%	2 0-2 5%	
Duration, in hours of moderate hypotension*	3-4 hrs	3 5-4 5 hrs	1 5-2 hrs	2-3 hrs
Duration in hours of drastic hypotension*	1 5-3 hrs	1-1 5 hrs	2-2 5 hrs	1-1 5 hrs
No of dogs reversible† to infusion	2	6	2	11
No of dogs irreversible‡ to infusion	6	28	12	54
Total no of dogs	8	34	14	65

\* Despite variations in the exact level of hypotension, the dogs were kept in a comparable state by regulating the bleeding so as to produce in all the animals the same degree of slowing of the omental circulation.

† By reversible is meant a sustained rise of blood pressure and a recovery of the omental circulation for 2-3 hours after the infusion.

‡ By irreversible is meant a lack of sustained response of the omental circulation and an unsustained rise of blood pressure which lasted not longer than 1-2 hours.

The majority of the 65 dogs, 48 in number (Typical Group) developed circulatory failure after being in the hypotensive state (moderate + drastic) from four to six hours. A smaller number of nine dogs (Unstable Group) proved to be very susceptible to the bleeding and reached hypotensive levels after being bled as little as 1.5 to 2.0 per cent of their body weight. These dogs could not be kept even at moderate hypotensive levels for any extended period of time. Their blood pressure had a tendency to fall despite the restoration throughout a period of two to three hours of their entire blood volume by repeated small infusions. A third small number of eight dogs (Resistant Group) proved to be highly resistant and required bleedings of more than 4 per cent of their body weight to lower their blood pressure to sustained hypotensive levels. These dogs had to be bled repeatedly until a point was reached where their blood pressure tended to fall abruptly. Unless almost their entire blood volume was then restored, they died within 15 to 20 minutes.

The omental changes were essentially the same in the three groups of dogs except for the time required for the different stages to appear and the degree to which the changes developed. The accompanying charts, summarizing the data of four selected protocols of irreversible dogs, illustrate the reactions of eight selected criteria representing the condition of the capillary circulation throughout the syndrome. The extent of deviation from the normal, which is represented by a base line, is expressed by the relative heights of the vertical lines. At the bottom of each chart is a curve of the carotid blood pressure, presented at five-minute intervals. The successive bleedings and infusions are recorded as black squares below the blood pressure curve.

## I—TYPICAL GROUP

In this category were the 48 dogs of which the total blood loss amounted to 3 to 4 per cent of their body weight. These dogs were maintained at hypotensive levels for 4.5 to 6 hours, the final one to two hours being at drastic levels (below 45 Mm). The relative lengths of moderate and drastic hypotension were varied, 34 dogs being subjected to moderate (55–65 Mm) for 3.5 to 4.5 hours, followed by a period of 1 to 1.5 hours of drastic hypotension (40–50 Mm), while 14 were subjected to moderate for 1.5 to 2 hours, followed by a relatively longer period of 2 to 2.5 hours of drastic hypotension.

Out of the 48 dogs treated in this way eight recovered after being infused with the blood withdrawn. In these the omental circulation maintained the normal unidirectional flow, although very much slowed during the terminal stage. The vasomotion of the metarterioles and precapillaries disappeared but the epinephrine responsiveness, which became hypernormal during the initial stages after the bleeding, never fell below the normal threshold value obtained prior to the bleeding.

The remaining 40 dogs proved to be irreversible to the final blood infusion. The protocols of two of these, as representatives of this group, are given below, that of Dog 71 being given in detail and that of Dog 64 in part. The times given in the protocols refer back to the zero time at the start of the experiment, as noted in the charts.

## A—PROTOCOLS OF DOGS 71 AND 64

Dog 71—(Chart 1. Wt 105 Kg. Morphine sulfate, 12 mg/Kg, subcutaneous. Initial B. P., 110–150 Mm Hg. Omentum exposed 30 minutes later. Capillary circulation slightly hyperemic, returning to normal in few minutes. Metarterioles and precapillaries showed normal vasomotion with phases alternating at intervals of 45 secs to 2 mins. Threshold response to epinephrine, 1/6 million.)

*a Changes Initial to Hypotensive State (0–1.5 hrs after start of bleeding)*—The earliest reactions to blood loss occurred while the blood pressure was falling from 110 to 85 Mm Hg and are not indicated on the chart. After the first bleeding of 20 cc/Kg the larger arteries (75–150  $\mu$  in diameter) underwent constriction (from 75 to 65  $\mu$ ). After the second bleeding of 10 cc/Kg (totaling 3 per cent of body weight) their caliber was further reduced to about one-half to one-third the normal size (45–50  $\mu$ ). Their accompanying veins constricted after the second bleeding from 100 to 86  $\mu$ . These arteries and veins remained constricted throughout the syndrome and relaxed only when the final large infusion was made 6.5 hours later.

The following appears on the chart and deals with the capillary bed proper and with its adjacent arterioles (40–50  $\mu$ ) and muscular venules (45–60  $\mu$ ). The reactions of the selected criteria are presented separately in the order of their appearance.

1 *Vasoconstriction*—The muscular venules (50–60  $\mu$ ) constricted to 40–45  $\mu$  within 15 minutes after the first bleeding. The arterioles (40–50  $\mu$ ) began to be partially narrowed during the second bleeding (from 40 to 30  $\mu$ ) and, by the time the blood loss had reached a total of 3 per cent, became further constricted to 20  $\mu$  and varicose. This was the maximal constriction observed during the syndrome.

2 *Vasomotion*—That of the metarterioles was augmented shortly after the second bleeding. By the end of the first hour, the constrictor and dilator phases alternated as

rapidly as two complete cycles per minute. During the second hour, the vasomotion of the precapillaries was especially prominent.

3 *Response to Epinephrine*—The responsiveness to epinephrine rose at about the same time that vasomotion became augmented. After the second bleeding the threshold response was 1:13 million.

4 *Capillary Flow*—There was little change in the rate of flow although the flow became increasingly intermittent during the second hour in accordance with the augmented vasomotion.

5 *Venular Flow*—This remained almost unchanged. After the third bleeding many of the direct shunts between arterioles and veins became considerably narrowed. There was a definite slowing of the flow in the larger veins.

b *Changes during Hypotensive State after Third Bleeding (15–65 hrs after start of hemorrhage B.P., 65 Mm Hg)*—The progressive changes in the capillary bed during the remainder of the posthemorrhagic syndrome could conveniently be divided into three stages. When the blood pressure fell to moderate hypotensive levels, there was an appreciable slowing of the flow but the *hyperreactive* aspects of the syndrome continued for about four hours, during which 2 cc/Kg was infused to hold the blood pressure within the range of 55–65 Mm after four hours of moderate hypotension. The blood pressure was further lowered by a small bleeding. This introduced a more severe curtailment of flow and the development of a *transitional* stage in which the hyperreactivity of the vessels was gradually lost over a period of about an hour. Finally, during the last half hour of drastic hypotension and for 20 minutes after the final infusion of whole blood had been started, the syndrome passed into a *hyporeactive* stage.

#### HYPERREACTIVE STAGE

1 *Vasoconstriction*—The arterioles maintained the constricted state noted during the early compensatory reactions. The venules remained moderately narrowed until the beginning of the fourth hour, when they began to distend from 40 to 45  $\mu$ .

2 *Vasomotion*—The augmentation attained one cycle every 15 to 20 seconds, with the constrictor phase lasting about two-thirds of each cycle. Towards the end of the fifth hour, the length of the dilator phase became progressively increased.

3 *Response to Epinephrine*—During the last hour of this stage (6th hour) the hyperreactivity of the metarterioles and precapillaries fell slightly from 1:13 million to 1:10 million.

4 *Capillary Flow*—During the third and fourth hours the rate of flow remained unchanged. Most of the flow was restricted to the central channels by the constriction of the precapillaries.

5 *Venular Flow*—The venular flow began to fall off within 30 minutes and diminished appreciably toward the end of the fifth hour.

#### TRANSITIONAL STAGE

1 *Vasomotion*—That of the metarterioles diminished, the dilator phase becoming increasingly longer and the constrictor phase very short.

2 *Venular Caliber*—The venules (45–60  $\mu$ ) became dilated from 45  $\mu$  to 65  $\mu$  and exhibited markedly thin walls.

3 *Venular Flow*—This became increasingly sluggish.

4 *Capillary Flow*—A marked slowing became evident, especially during the fifth hour. This was accompanied by a developing deficiency of outflow through the venules. The diminished vasomotion of the metarterioles and the longer periods of dilatation of the precapillary sphincters were accompanied by an increase in the number of capillaries containing a flow. This increased distribution of blood, without a corresponding increase of the amount of inflow, resulted in a significant slowing of the flow, especially on the venous side of the bed, which was intensified by the atonic state of



the muscular venules. The flow in the larger omental veins became considerably reduced and was now maintained mostly by the few arteriovenous anastomoses which still were open.

5 *Response to Epinephrine*—Within 20 minutes after the curtailment of the capillary flow this fell from the hyperreactive response of 1 10 million to a relatively normal response of 1 4 million.

#### HYPOREACTIVE STAGE

1 *Vasomotion*—This ceased in the metarterioles with the dilator phase persisting. That of the precapillaries stopped 20 minutes later.

2 *Response to Epinephrine*—There was only a fleeting constrictor response to 1 2 million.

3 *Venules and Venular Capillaries*—These became distended by backflow from the congested veins.

4 *Arterioles*—The relaxation of the arterioles developed later than in the venules and the previously very slow forward flow was replaced by a pulsatile movement of the blood.

5 *Stagnation of Blood*—Many of the capillaries and venules were stagnant.

c *Changes Following Restoration of Blood Volume by Infusion*—At this point (after 45 hours of moderate and 15 hours of drastic hypotension) a drip infusion was started and continued until all of the blood previously withdrawn had been restored. During the 30 minutes that the infusion lasted the blood pressure rose to 90 Mm Hg. When about 8–10 cc/Kg (one-third of the blood to be infused) had been given, the constricted omental arteries gradually resumed and maintained their normal caliber. The larger veins relaxed at about the same time but became abnormally dilated during the ensuing 50–60 minutes. The blood pressure then again fell to hypotensive levels.

There was no improvement in the peripheral circulation until about 20 minutes after the infusion was started and the blood pressure had risen to about 80 Mm Hg. At this time the capillary flow became moderately speeded but slowed down again after 40–50 minutes. The previously dilated arterioles became slightly constricted\* and there was a faint return of vasomotion of the metarterioles. The epinephrine response to 1 4 million became more evident than before, and this degree of responsiveness lasted for 30 minutes when it fell off rapidly.

About one hour after termination of the blood infusion, while the blood pressure was still about 70–80 Mm Hg, the capillary flow began to slow down and became almost completely stagnant as the blood pressure slowly dropped below 70 Mm. Backflow from the larger veins into the capillary bed now became prominent and a generalized stagnation occurred with the death of the dog.

Dog 64—(Chart 2. Wt 9 Kg. Morphine sulfate, 12 mg/Kg, subcutaneous. Initial B. P., 120–130 Mm Hg.)

The omental changes in the chart of Dog 64 were closely similar to those of Dog 71. This protocol is presented because it illustrates particularly well that blood pressure and peripheral circulatory curtailment do not go hand in hand. Between the fourth and fifth hours, when the blood pressure was relatively high, varying between 65 and 80 Mm, there was a decided slowing of the capillary flow and a more drastic slowing of the venular flow. A similar circulatory curtailment in Dog 71 did not occur until the blood pressure had dropped to 50–55 Mm Hg. Moreover, later, during the fourth

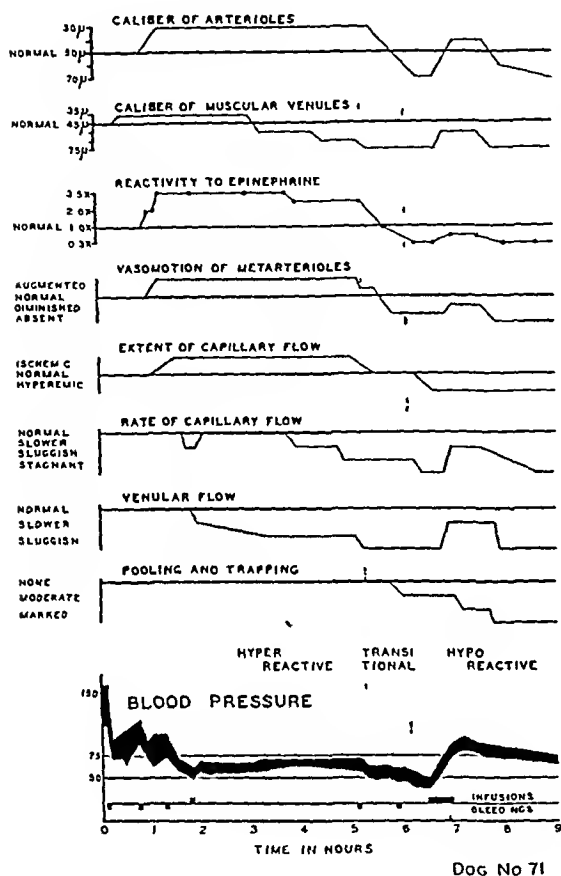
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\* Only occasionally do the arterioles in the irreversible stage of shock respond to the infusion by a temporary moderate constriction, as in the above case. As a rule, the dilatation of the arterioles is one of the final evidences of irreversibility, and, following infusion, they become still further dilated.

## CIRCULATION IN GRADED HEMORRHAGE

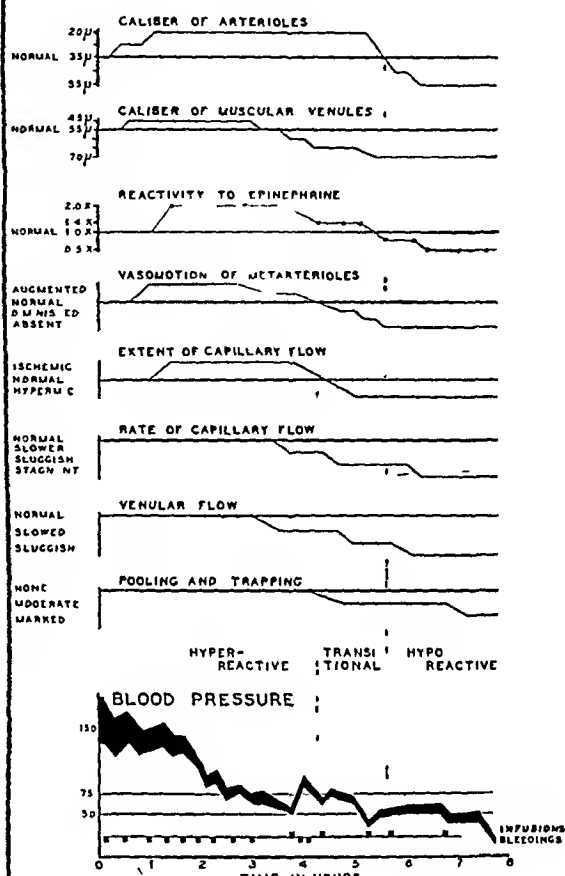
and fifth hours, when blood infusions of 3-4 cc/Kg were given, the venular caliber, vasomotion, venular and capillary flow remained subnormal despite the temporary rise of the blood pressure by 20-30 Mm which occurred with each infusion. During the sixth and seventh hours the infusion of all the blood withdrawn (by three separate injections) had no appreciable action on the peripheral circulation, although it kept the blood pressure from falling precipitously

CHART 1



Dog No 71

CHART 2



Dog No. 64

CHART 1—Tabulation of protocol of Dog 71, representing typical group. The chart shows the changes in the capillary bed of the omentum in their relations to blood pressure, bleedings and infusions in a dog which became irreversible to infusion of the blood withdrawn. The upper eight rows represent changes in selected functional criteria.

The deviations from the normal are expressed by the relation of a continuous graph line to the normal base line. In all the criteria, except for epinephrine reactivity, this represents changes recorded continuously by direct observations. The epinephrine reactions were obtained at intervals, and each is recorded on the chart by a solid circle.

The blood pressure curve represents carotid readings at five minute intervals, each with maximum and minimum values obtained during a 30 second period. The horizontal lines at 75 and 50 Mm, respectively, represent shock levels of hypotension.

CHART 2—Tabulation of protocol of Dog 64, also of typical group. It illustrates the unreliability of blood pressure as a criterion of circulatory changes. Explanatory legend same as in Chart 1.

### B—ANALYSIS OF CHANGES IN OMENTAL CIRCULATION IN DOGS OF THE TYPICAL GROUP

The two protocols, representing the 40 irreversible dogs of this group, demonstrate that definite circulatory changes occur as the hemorrhagic syndrome progresses towards irreversibility. In all the cases, the initial large bleedings of 2 to 3 per cent of body weight were accompanied by a vasoconstriction of the larger arteries and veins and a restriction of the omental circulation with an augmented vasomotion of the metarterioles and precapillaries. Throughout this period the epinephrine reactivity was hyper-

normal and, in some cases, rose from a normal threshold level of 1.4 to 6 million to as high as 160 million. This hyperreactive state generally persisted for three to five hours after the initial bleedings.

During the period of hypotension, the subsequent small bleedings were followed not only by the mechanical factor of a pronounced slowing of the flow but also by a progressive deterioration of the functional aspects of the bed. The earliest manifestation of this was venular dilatation. The other outstanding effects, *viz*, diminution of the vasomotion and the fall of epinephrine responsiveness, varied as to time and degree in different dogs and are discussed below.

The majority which tolerated a total blood loss of 3 to 4 per cent and a relatively long period of moderate hypotension resembled Dogs 71 and 64. This was also the case for six of the 14 dogs with a short moderate hypotension which were bled expressly to bring them into drastic hypotension. The remaining eight showed a spontaneous tendency for the blood pressure to fall and did not require bleeding to bring them early into drastic hypotension. These eight maintained the vasomotion and the normal epinephrine reactivity of their metarterioles almost to the time of death, thus indicating that at least some of the physiologic properties of the capillary bed had not deteriorated. Their circulatory failure presented essentially the effects of a mechanical type. The ensuing circulatory failure may be attributed, in large part, to a marked trapping and pooling of blood in the capillary bed.

A few relatively unstable dogs were maintained at low hypotensive levels of 40 to 50 Mm for as long as 2 to 3.5 hours by repeated small infusions (3-4 cc/Kg). In spite of the infusions, the blood persisted in pooling and stagnating in the peripheral circulation and there developed a backflow into the capillaries which finally became so intensified as to prevent the return of adequate amounts of blood from the tissues. With this type of extreme hypotension the syndrome became irreversible to infusion. Although neither the epinephrine reactivity nor the vasomotion was completely depressed, the restoration of the blood withdrawn did not bring the stagnant blood in the bed into active circulation and the dogs died within 20 to 40 minutes after the infusion.

Another interesting feature was the variation in the effect of the sustaining small infusions on the recovery of some of the physiological functions of the capillary bed. Dog 64 was an example of those cases in which the small infusions exerted no appreciable effect on the capillary bed. However, in other dogs, the capillary bed did react, particularly in regard to the epinephrine reactivity, which rose temporarily, although progressively less, with each sustaining infusion. Vasomotion, on the other hand, when once subnormal was never observed to recover as long as the hypotension remained at drastic levels.

#### II—UNSTABLE GROUP

This included nine dogs which were unusually susceptible to bleeding. Considerable care had to be taken while bringing them into hypotensive levels

# CIRCULATION IN GRADED HEMORRHAGE

to prevent a precipitous fall of their blood pressure. They also had to be frequently primed with small infusions in order to maintain them in hypotension for any extended period. Only one of the nine dogs was found to be reversible by blood infusion. This dog had stopped breathing and required a massive blood infusion before respiration reappeared. The depressed omental

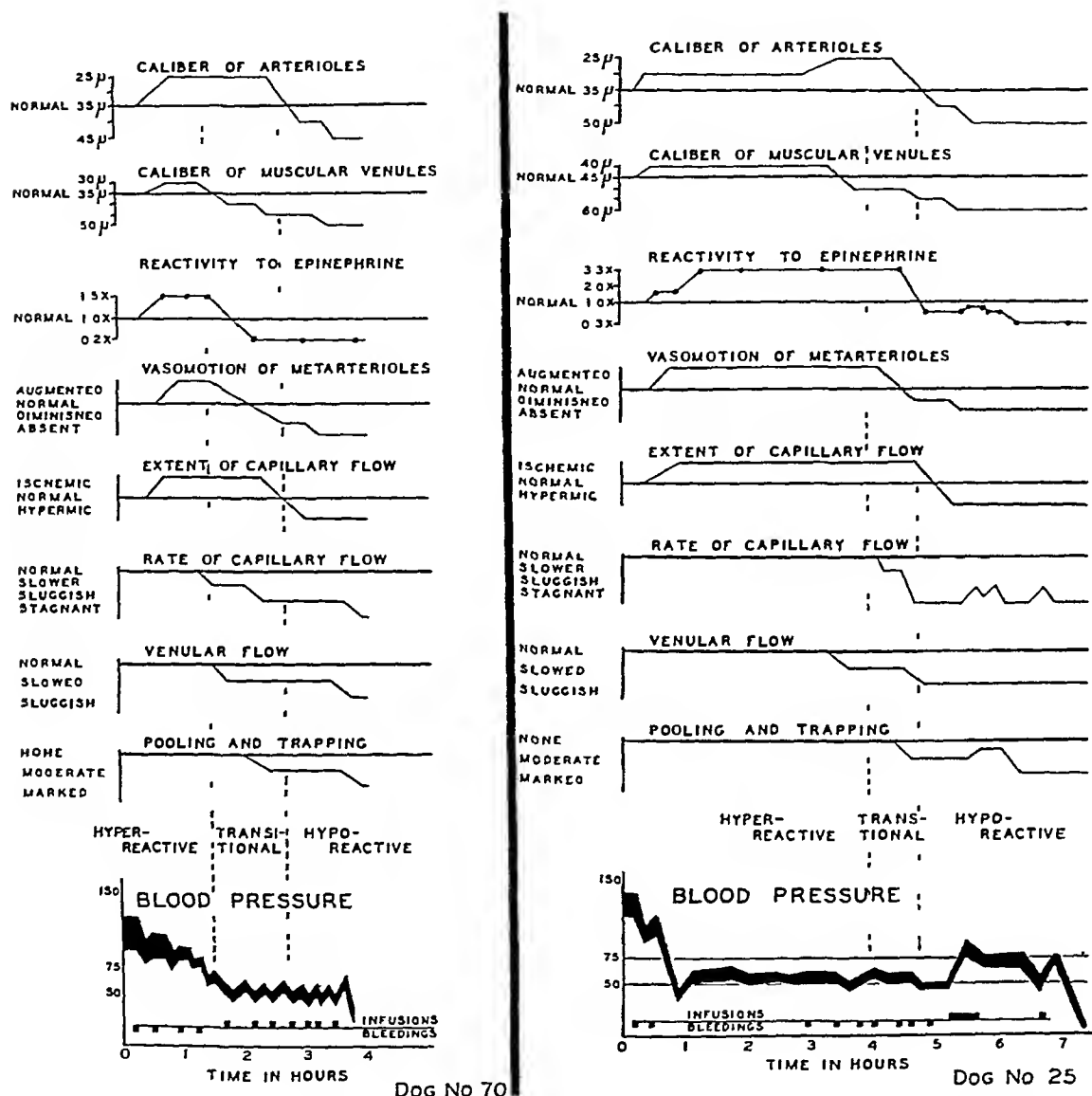


CHART 3—Tabulation of protocol of Dog 70, representing unstable group. Explanatory legend same as in Chart 1.

CHART 4—Tabulation of protocol of Dog 25, representing resistant group, which requires frequent bleedings. Explanatory legend same as in Chart 1.

circulation was restored to normal within 15 minutes after the infusion had been made.

Dog 70—(Chart 3. Wt 12 Kg. Morphine sulfate, 12 mg/Kg, subcutaneous Initial B. P., 95–120 Mm. Hg.)

Prior to bleeding the epinephrine response was 1.4 million and the vasomotion recurred one cycle in two to three minutes. A blood loss of 285 cc (2.38 per cent of body weight) in four bleedings brought the blood pressure down to the 60–67 Mm.

range and appreciably slowed the flow through the bed. Within 15 hours after these bleedings the hyperreactive aspects of the circulation were disappearing. The venules became atonic and distended as early as the end of the second hour. Both the epinephrine reactivity and vasomotion, which had been only moderately enhanced, fell off rapidly during the early part of the third hour. The cessation of vasomotion was followed by an almost complete stagnation of the capillary flow. These changes rapidly produced a pooling and trapping of blood on the venous side of the bed as early as 25 hours after the initial bleedings and after only one hour of hypotension. Throughout the third and fourth hours, seven infusions of whole blood, each about 3 cc/Kg, were required to keep the dog from precipitously going into circulatory collapse. Although these temporarily sustained the blood pressure, none exerted any beneficial action on the peripheral circulation. Respiratory failure occurred during the latter half of the fourth hour, necessitating artificial respiration. The hyporeactive state persisted despite the infusion of the final 70 cc of blood and complete circulatory collapse occurred at the end of the fourth hour. Throughout the final 60 to 70 minutes, the omental circulation was practically at a standstill, except for a sluggish flow in the largest arteries and veins.

### III—RESISTANT GROUP

This included eight dogs which were highly resistant and required repeated bleedings to counteract the tendency of the blood pressure to rise out of the hypotensive range. The following is a summary of the protocol of Dog 25, which was selected as representative of this group.

**Dog 25**—(Chart 4 Wt 10 Kg Morphine sulfate, 12 mg/Kg, subcutaneous Initial B P, 130–140 Mm Hg)

A blood loss of 3 per cent of the body weight brought the blood pressure down to moderate hypotension (55–65 Mm) which persisted for over two hours. Throughout this period the flow through the bed was rapid, although restricted to the central channels by the hyperactivity of the vasomotion. At the beginning of the third hour, the blood pressure showed a tendency to rise, and during the ensuing two hours seven bleedings, of 2 to 3 cc/Kg each, had to be made to prevent it. Deterioration of the capillary circulation did not develop until after the fourth hour, when the capillary blood flow began to slow down. Within the next 40 minutes, all of the selected features were depressed below normal. Two small bleedings (3 cc/Kg) brought the blood pressure to drastic levels of hypotension (42–52 Mm), and the capillary circulation to a sluggish state. This brought about chiefly a marked pooling of blood in the venules. At this point (after 45 hours of hypotension) an infusion, restoring the blood volume (39 cc/Kg), raised the blood pressure but had no sustained beneficial action on the peripheral circulation. The blood pressure remained above 70 Mm for about 15 hours, when the dog went into cardiac and respiratory failure and died. Such animals are extremely difficult to recover by infusion.

**DISCUSSION**—A prerequisite for any experimental study of the capillary circulation is the establishment of adequate criteria for determining the normal functional state of the vascular bed. Too much stress cannot be placed on the necessity of rigid adherence to precautionary measures for preventing the observational technic from interfering with the normal reactivity of the sensitive, organized systems of the capillary bed. A discussion of such measures is given in a previous publication.<sup>8</sup>

The omentum was elected in the present study because, in contrast to the cutaneous tissue, its circulation is maintained throughout the greater part of the hemorrhagic syndrome. It has been claimed, because of the pale and ischemic appearance of the omentum at autopsy, that this structure is not the logical site for the study of significant vascular changes in circulatory collapse. On the other hand, in the present study, the successive changes in the omental circulation have been shown to serve as an excellent end-point for evaluating the progressive nature of the syndrome. No attempt has been made at an analogy between the circulatory changes observed in the omentum and those occurring in other tissues. However, the findings are suggestive in that they bring out the type of change occurring in a typical capillary bed as a result of the ischemia produced by hemorrhage. In previous studies<sup>6</sup> on the frog and mouse it was shown that the type of capillary bed described in this paper is characteristic of those in the skin, striated muscle, intestinal submucosa and the pancreas. Hence although the omental changes may not be of direct significance in precipitating the circulatory failure, in all likelihood they reflect conditions which occur in other organs where such changes may be of paramount importance.

Wiggers<sup>14</sup> recommends that whenever possible a differentiation be made between initiating and consequential mechanisms during the shock syndrome. The results presented in this paper, insofar as the capillary bed is concerned, point to the appearance, in succession, of two outstanding mechanisms leading to so-called irreversible hemorrhagic shock. The initiating mechanism is that of widespread vasoconstriction, which follows immediately and is proportional to the blood loss. The consequential mechanism consists of a series of changes which result from the curtailment of the blood flow through the capillary bed.

The initiating mechanism of vasoconstriction is well recognized and, by some, has been taken as the prime feature in shock. Vasoconstriction in the microscopic vessels of the skin following hemorrhage has been observed in dogs by Meek and Eyster,<sup>9</sup> and Mann,<sup>10</sup> in rabbits by Levinson and Essex,<sup>11</sup> and in rats by Chambers, Zweifach and Lowenstein.<sup>12</sup> In our present study on the dog's omentum, vasoconstriction was also observed only when the blood loss amounted to about 3 to 3.5 per cent of the body weight.

On the basis of changes in the capillary circulation following hemorrhage it was possible to distinguish between two discrete types of peripheral circulatory failure. In our<sup>16</sup> studies on acute hemorrhage it was shown that the initiating mechanism of excessive and rapid blood-loss is emphasized to such a degree that circulatory collapse occurred without the development of other consequential mechanisms in the capillary bed. This involved a purely mechanical type of circulatory failure in which vasoconstriction of the larger blood vessels and lowered blood pressure by themselves produced the semi-stagnation of the flow and the pooling of blood in the capillary bed. This type of circulatory failure is completely reversible by adequate blood infusion.

Our data on the effects of acute hemorrhage conform with the results

of Page and Abell<sup>2</sup> from their experiments on circulatory failure in dogs and cats caused by the acute removal of blood. They obtained similar results with the use of the venous tourniquet and generalized that circulatory failure in shock is primarily a result of excessive vasoconstriction. They, thus, considered the initiating mechanism as the only important factor in shock. However, it should be noted that their tourniquet experiments involved venous ligatures on all four limbs. This induces considerable swelling of all the limbs and the results could be interpreted from the same point of view of excessive fluid loss as obtains in acute hemorrhage.

The introduction of consequential factors in hemorrhagic shock occurs by maintaining the dogs, through the use of small infusions, in a state in which a sluggish capillary circulation persists over a protracted period of time. The ensuing type of circulatory failure involves a progressive deterioration of those mechanisms which maintain the functional integrity of the capillary bed. From our observations on the omentum it was found that, with graded hemorrhage, the initial, compensatory hyperreactivity of the syndrome persists as long as the blood pressure does not fall below the level needed to maintain a continuous peripheral flow. The consequential mechanism producing the hyporeactive stage comes into play when the blood pressure is maintained for at least 2 to 2.5 hours at levels at which the capillary circulation is slowed sufficiently to impair the outflow through the venules.

In the present study dependence was placed on the duration rather than on the degree of hypotension required to bring about irreversibility. Our results indicate that this produces a more standardized type of shock, and agree with the findings of Wiggers and Werle.<sup>17</sup> With the omental circulation as a guide, the syndrome was further standardized by bleeding all of the dogs until the flow through the capillary bed was significantly retarded, but not stagnant. The maintenance of this condition for two to three hours set into play local mechanisms which, under normal conditions, would act to increase the blood flow through the tissue (diminished vasomotion with the dilator phase predominating, reduced responsiveness to epinephrine, thereby presumably reducing the response of the muscular elements of the capillary bed to nervous stimuli, and the opening up of numerous capillary channels to the circulation). These changes in the capillary bed may be attributed to the piling up of metabolites in the tissues. Moreover, when the supply of blood and the propelling force are deficient, the opening up of the capillary bed for the reception of increased amounts of blood aggravates the general situation. The result is twofold. The drainage of the blood from the capillary bed continues to be faulty, and the inadequate and severely strained hemodynamic set-up is subjected to further strain by having a greater number of vessels through which to drive the blood. These conditions serve to bring about a further disorganization of the peripheral circulation, a prominent feature of which is atony of its muscular components. A vicious cycle of events is thus initiated through the interaction, on the one hand, of a trapping

and pooling of blood in the peripheral vessels and, on the other, of a disturbed metabolism of the tissues

The terms "trapping" and "pooling" have been used to denote the progressive sequestration of blood from the active circulation. Fine, Seligman and Frank,<sup>18</sup> using radioactive tagged plasma-proteins, have offered evidence that the "lost" blood in the syndrome is sidetracked into inactive capillary vessels and not lost through increased capillary permeability. Our studies offer visual evidence for this and indicate that trapping and pooling develop on the venous side of the capillary bed during the hyporeactive stage of the hemorrhagic shock syndrome. Trapping occurs as a result of the inadequate driving force for propelling the blood through all of the vessels, so that appreciable amounts of blood are left to stagnate in many capillaries which are by-passed by the active circulation. Pooling occurs subsequently with the failure of the most important peripheral, integrative factor of the capillary bed, *viz*, the vasomotion of the metarterioles and of the pre-capillaries. The capillary bed now becomes an inert network of vessels with no active rôle in the distribution of blood and in its return from the tissues.

With the loss of the integrative functional activity of the capillary bed, the outflow of blood through the venules becomes disproportionately reduced with respect to the arteriolar inflow. There thus accumulates in the capillary bed an ever-increasing proportion of the blood. The trapping and pooling, though small, are sufficient to intensify the oligemia until circulatory collapse ensues. This pooling does not necessarily indicate the accumulation of more than the normal amount of blood in the capillary bed, the amount at death being actually less than that normally present.

Circulatory collapse, following the development of hyporeactivity in the irreversible dogs, is essentially the result of a discrepancy between the volume of the circulating blood and the capacity of the vascular system. The changes in the omentum suggest two possible mechanisms which can take part in precipitating the circulatory failure. These are illustrated in Chart 5, which is a diagrammatic presentation of the outstanding changes representative of all the dogs studied. One set of changes emphasizes an intensification of the oligemia through pooling and trapping in the capillary bed (note sequence of changes on right side of the figure). The other set of changes intensifies the oligemia by an increase in the capacity of the vascular tree through the deterioration of the peripheral mechanisms for restricting the blood flow through the capillary bed (note sequence of changes on left side of the figure). When a group of dogs are bled, so as to produce circulatory failure, both types of circulatory changes develop, regardless of the hemorrhagic procedure used. The mechanical type of failure predominates when the degree of hypotension and the blood-loss factor are emphasized. On the other hand, the hyporeactive type of failure predominates when, as in the present study, the duration of hypotension is emphasized.



## SUMMARY

Characteristic indices in the capillary bed of the omentum of dogs subjected to graded hemorrhage under morphine have made it possible to identify successive stages of the syndrome leading to a state in which the dogs become irreversible to the restoration of their blood volume with whole blood. These stages are an initial hyperreactive stage, an intermediate transitional stage and a terminal hyporeactive stage.

Under the conditions of generalized ischemia during hemorrhagic shock, the vessels of the capillary bed undergo progressive physiologic changes expressed by an inactivation of the muscular vessels of the bed, with loss of their responsiveness, and a disorganization of the peripheral circulation.

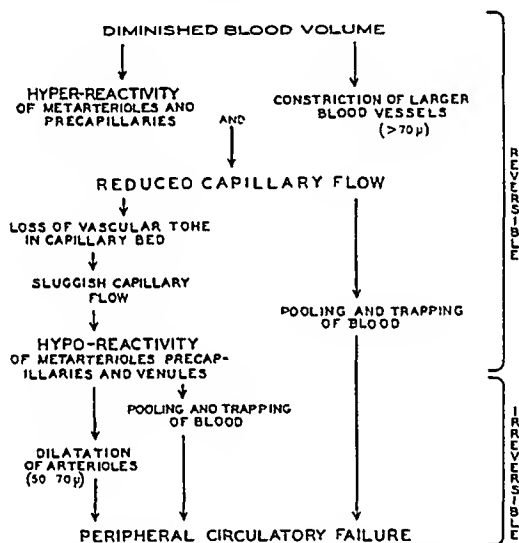
CIRCULATORY CHANGES IN OMENTUM OF DOGS  
SUBJECTED TO GRADED HEMORRHAGE

CHART 5.—On right side of chart are indicated changes resulting from extreme blood loss (greater than 4% of body weight) with little or no hyporeactivity. On left side of chart are indicated changes resulting from less extreme blood loss (3-4%) with development of a hyporeactive state before circulatory failure.

This is in contrast to the reactions of the larger blood vessels, which maintain an active state of constriction until shortly before death.

It was possible to distinguish in the capillary bed between two clear-cut types of changes during the progress of the syndrome. The first involves a purely mechanical factor which arises from the lowered blood pressure and from the vasoconstriction of the larger blood vessels. The absence of a sufficient propelling force induces a marked slowing of the capillary flow and the pooling of blood in the bed. This is characteristic of rapidly induced drastic hypotension and tends to be reversible to the restoration of the blood lost. The second type, which occurs when the drastic hypotension is sufficiently prolonged, involves a progressive deterioration of the functional

integrity of the capillary bed, *i e*, loss of arteriolar and venular tone, of vasomotion, and of responsiveness to epinephrine

### CONCLUSIONS

From our observations on the peripheral circulation of the omentum, a significant finding is that the development of irreversibility to infusion is associated with a hyporeactive state of the functional aspects of the capillary bed. The hyporeactivity *per se* does not necessarily imply irreversibility. The hyporeactivity must be maintained for a protracted time. The actual end-point indicating irreversibility is the failure of the hyporeactive capillary circulation to respond to test infusions. Restoration, at this stage, of all the blood previously withdrawn may mechanically set up a flow through the bed but will not restore the physiologic reactivity of its muscular components. The significance of the changes observed in the capillary bed is further demonstrated by the fact that they reflect the progressive deterioration of the animal throughout the hemorrhagic shock syndrome.

We wish to acknowledge the very able assistance of our laboratory technician, Leon Dziorney.

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# CONDYLOMATA ACUMINATA

TWO HUNDRED CASES TREATED WITH PODOPHYLLIN

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CONDYLOMATA ACUMINATA not only are pathologic "nuisances" but occasionally they reach proportions which constitute serious clinical problems. Reliable statistics regarding their incidence are not available but it is generally agreed that they are extremely common. The fact that 180 individuals with typical lesions were seen by us during the past nine months adds proof to this contention. The great variety of therapeutic measures which have been recommended illustrates the inadequacy of most methods of treatment. The purpose of this report is to present the dramatic results which we have obtained with podophyllin. There is reason to believe that this drug may be a "specific" for condylomata acuminata.

The etiology of these growths remains unknown. They present raspberry, cauliflower or cockscomb masses, which are soft, red or cyanotic, often friable, and may be sessile, pedunculated or attached by a broad base. They must be differentiated from carcinoma and condylomata lata of syphilis, but this usually is not difficult. Mixed lesions may occur and complicate the clinical picture.

Condylomata acuminata have been described in many locations, usually on or near the genitalia, and have been given the misnomer "venereal warts." In the present series, they were found on the penis, the labia, the fourchette, lining the vagina, at the urethral meatus, around the anus, on the perineum and on the scrotum (Table I). They had been present for one day to eight months, with the average duration three months. All of these patients were less than 36 years of age, and 90 per cent were white.

Podophyllin is a powder which varies in color from light brown to greenish-yellow, and turns darker when subjected to heat or light. It is an irritant and active purgative and is the basis of several proprietary "liver pills." Various strengths of podophyllin have been tried in the treatment of condylomata acuminata but a 25 per cent suspension in mineral oil has proved most efficacious and has been used in the 200 cases which comprise this report.

The podophyllin in oil is applied with a cotton swab to the surface of the lesions. This is a painless procedure and there is no immediate reaction. Anesthesia is not required, because of the viscosity of the oil and close approximation of normal tissues (*e g*, redundant prepuce) it is impossible to keep the podophyllin confined to the condylomata, but in most instances this does not alter the therapeutic effect of the drug. Within

a few hours the growths become blanched, and 24 to 48 hours later they appear necrotic. The condylomata begin to slough on the second or third day and promptly disappear. No ulceration or scarring is left at the bases. The adjoining normal tissue usually is unaffected even though it has been exposed to the same medication. Most patients experience no discomfort during the entire process and only rarely is sedation necessary. There have been no systemic reactions to any of the 249 treatments employed in this group of 200 patients. This type of therapy is so simple and the clinical courses so uneventful that it is performed in the clinic or office and hospitalization is unnecessary. The minimum loss of time to the patient has made it especially valuable among military personnel.

No satisfactory explanation of the more or less specific action of podophyllin on the condylomata is possible at this time. The most logical assumption is that the irritating power of the drug produces spasm of the small vessels, which in turn causes ischemia, necrosis and sloughing. The blood supply of the condylomata apparently is more susceptible to the 25 per cent suspension than that of the more viable, adjoining, normal tissues. The podophyllin also seems to dehydrate the condylomatous masses. Irrespective of the exact physiology involved, the dramatic results obtained in these cases indicate that podophyllin is of tremendous value in the treatment of condylomata acuminata.

All of the 200 patients in this study were cured regardless of the number, size, location or duration of the growths. Only one application of podophyllin was needed for 81.5 per cent, while an additional 14.5 per cent were cured by a second treatment. No one required more than four applications of the drug. In 72.5 per cent of the cases, complete recovery occurred within four days, while only 6.5 per cent required more than eight days for disappearance of the growths. No discomfort was experienced by 83.5 per cent of the patients and only 2 per cent required any sedation (Table I).

Because of the movements of military organizations, complete follow-ups have been impossible. There have been nine known recurrences of the condylomata (4.5 per cent) but others may have occurred. In each of these nine cases, response was prompt to additional similar treatment with podophyllin. Inasmuch, as the etiology of the initial lesions is unknown, there is reason to anticipate recurrences or new growths after *any* type of therapy. The causative factors no doubt continue to exist in many cases despite prompt disappearance of the original growths. Initial and recurrent lesions respond equally well to podophyllin, and this appears to be the treatment of choice for all condylomata acuminata.

The minor variation in clinical courses with lesions in different locations are demonstrated by the following group analyses (Table I).

*Penis*—A total of 168 patients had condylomata acuminata on the penis. The only instances of associated venereal diseases were in this group. Nine patients had acute gonococcal urethritis and five had chancres. These were

CONDYLOMATA ACUMINATA

treated by accepted methods and did not influence the course of the condylomata or result in recurrence

The number of growths in each case varied from single lesions to clusters of as many as 25 pedunculated tumors with the average six. These varied in size from 2 Mm in diameter to conglomerate masses covering the glands or filling the coronal sulcus. Most of the discrete lesions were 0.5 to 1.0 cm in diameter.

TABLE I  
 ANALYSIS OF 200 CASES OF CONDYLOMATA ACUMINATA TREATED WITH PODOPHYLLIN

Location	Total Cases	No of Treatments				Days Until Cured			Pain			V D		Recurrence
		1	2	3	4	2-4	5-8	More	None	Mild	Req Sed	Lues	GC	
Penis	168	148 88 1%	16 9 5%	2	2	134 79 8%	30 17 8%	4	150 89 3%	18 10 7%	0	5	9	8
Female genitalia	15	9 60%	6 40%	0	0	7 46 6%	4 26 7%	4	2 13 3%	9 60%	4	0	0	0
Urethra	10	2 20%	5 50%	2	1	2 20%	5 50%	3	10 100%	0	0	0	0	1
Anus	4	3 75%	0	0	1	1 25%	2 50%	1	2 50%	2 50%	0	0	0	0
Male perineum	2	1 50%	1 50%	0	0	1 50%	0	1 50%	2 100%	0	0	0	0	0
Scrotum	1	0	1 100%	0	0	0	1 100%	0	1 100%	0	0	0	0	0
Total	200	163 81 5%	29 14 5%	4 2%	4 2%	145 72 5%	42 21%	13 6 5%	167 83 5%	29 14 5%	4 2%	5 2 5%	9 4 5%	9 4 5%

The condylomata were found most frequently in the coronal sulcus or at the frenulum but occurred at any point along the shaft or mucous membrane of the redundant prepuce (Fig 1). Four patients had been circumcised prior to the onset of the lesions, thus dispelling any claims that circumcision alone is adequate prophylaxis. Twenty patients had been treated previously with escharotics without complete disappearance of the growths.

Only one application of podophyllin was necessary to produce complete disappearance of all lesions in 88.1 per cent of these patients (Fig 2). Only four patients required more than two treatments. An interval of four to six days was employed between applications in these cases.

The condylomata had entirely disappeared and the sites appeared normal within four days in 79.8 per cent of the patients (Fig 2). An additional 17.8 per cent were well in five to eight days. Those patients who required repeated treatment automatically had longer intervals until cured.

No discomfort of any kind was noted by 89.3 per cent of the patients. The remaining 10.7 per cent had only mild burning. None of these required sedatives. The same patients (total of 18) had some degree of chemical balanoposthitis. All had very long prepuces. The balanoposthitis was mild and subsided quickly in all but three cases. The tissue reaction was severe in these three instances and, because of marked prepuccial edema, dorsal slit was done. This may not have been absolutely necessary. In each of

these three cases complete disappearance of the condylomata was found at operation and the balanoposthitis subsided promptly after surgical exposure of the glans. No balanoposthitis or edema has been observed since the patients have been advised to wash off the podophyllin 24 hours after its application.

Eight of our nine known recurrences were in this group. These appeared



FIG 1

FIG 2

FIG 1—Multiple condylomata in coronal sulcus and along mucous membrane of prepuce  
(Photograph by U S Army Signal Corps)

FIG 2—Same patient four days after single application of podophyllin in oil  
(Photograph by U S Army Signal Corps)

from one to six months later and in each case, one additional treatment caused disappearance of the lesions. Several patients have been followed nine months without recurrence or new growths.

Hospitalization was necessary only for the three patients who were subjected to dorsal slits.

*Female Genitalia*—Fifteen women had condylomata acuminata on the genitalia. Eight of these were pregnant. The growths have been known to fill the vagina and require cesarean section. This promised to be true in at least one of this group.

The lesions were confined to the labia in nine cases, to the fourchette in two patients and were scattered throughout the vagina in the remaining four. They varied in size from 0.5 cm in diameter to a condylomatous mass which filled the vagina of one patient who was eight months pregnant. In most instances four or five growths were present.

No patient in this group required more than two applications of podophyllin and 69.3 per cent were cured within eight days. The remaining four patients had disappearance of the condylomata in 9 to 14 days.

These patients experienced more pain than any other group. The four with diffuse vaginal involvement required codeine or morphine. Only two

patients, with lesions limited to the labia, had no discomfort. Sedation was necessary for only 12 to 24 hours.

No recurrences have been noted. Treatment of the condylomata did not disturb any of the eight pregnancies.

*Urethra*—Ten males had single lesions just inside the urethral meatus. These were 0.2 to 0.6 cm. in diameter. Only two were cured by one treatment. Urination caused premature removal of the podophyllin from the condylomata, thereby, necessitating repeated applications of the drug. Five patients were well after two treatments. Two patients required three applications and another needed four. An interval of four days was used between treatments.

Because of the prolonged therapy, only two patients were cured within four days. Five were well in five to eight days and the remaining three patients had disappearance of the growths in 9, 14, and 21 days, respectively. None of these ten patients had any pain.

One patient, whose condyloma disappeared after a single treatment, had a recurrence two months later. This disappeared after two treatments.

*Anus*—Four males had clusters of condylomata surrounding the anus at the mucocutaneous margin. Three were cured within one week after a single application of podophyllin. The fourth patient required four treatments, and was well in 16 days.

Two patients had no discomfort but the other two had mild burning pain for 24 hours. No recurrences have been observed in this group.

*Perineum*—Two patients had condylomata on the perineum, midway between the anus and the base of the scrotum. Three pedunculated growths, each 1 cm. in diameter, were present in one case, while the other presented two such lesions.

One patient was cured four days after one application of the drug and the other was well in ten days but required two treatments. No pain was experienced in either case. No recurrence has been observed in four months.

*Scrotum*—One patient had 25 discrete condylomata, each about 0.5 cm. in diameter, scattered over the left side of the scrotum. Two treatments (with an interval of four days) caused complete disappearance of all lesions in one week without discomfort. There has been no recurrence in three months.

COMMENT—Tomskey, Vickery and Getzoff have reported excellent results in the treatment of granuloma inguinale with podophyllin. Two such cases which failed to respond to other therapy at this hospital were cured promptly with 25 per cent podophyllin in oil.

The oil suspension and powdered drug have been used by us in removing excessive granulation tissue from surgical wounds with dramatic success. It appears to be far superior to the conventional silver nitrate in this respect.

Podophyllin has been of no value, however, in the treatment of typical, horny verrucae, of condylomata lata of syphilis or of benign rectal polypi.

This drug appears to be most efficacious in removing soft granulomatous tissues, and its clinical applications may not be exhausted. Further studies pertaining to additional therapeutic values of podophyllin are being conducted but as yet are inconclusive.



## SUMMARY

Podophyllin has been found to be unusually successful in producing prompt and complete disappearance of condylomata acuminata regardless of size, number, location or duration of the growths. The drug is best applied as a 25 per cent suspension in mineral oil. Anesthesia and hospitalization are not necessary. There is minimal time lost from any type of physical activity.

Most lesions disappear within four days after a single application of the drug. Growths within the urethra usually require two or more treatments. None of our patients required more than four topical applications.

No ulceration or scarring results and the surrounding normal tissue usually is unaffected by the drug. In isolated cases of extensive application under long prepuces some balanoposthitis may develop but thorough washing 24 hours after treatment promises to prevent this and not interfere with the end-result.

The convalescence is usually entirely painless but some patients, especially those with extensive involvement of the vagina, may require sedation.

Recurrences or new growths are to be expected since the etiology of condylomata acuminata remains unknown, but these, likewise, respond quickly and completely to the same treatment.

Podophyllin appears to be capable of destroying most types of granulomatous tissue and additional clinical applicability probably will be forthcoming.

The dramatic results obtained in this series of 200 patients with condylomata acuminata on the penis, female genitalia, perineum, scrotum, urethra and anus, and the simplicity of the treatment with podophyllin, prompt us to recommend more general adoption of this type of therapy.

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## TRANSACTIONS OF THE AMERICAN SURGICAL ASSOCIATION

MEETING HELD AT CHICAGO, ILL

MAY 3-4, 1944

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### ADDRESS OF THE PRESIDENT

#### THE STATE OF THE ASSOCIATION

FREDERICK A COLLER, M D

ANN ARBOR, MICH

THE AMERICAN SURGICAL ASSOCIATION is sixty-five years old today. At no time in its distinguished and illustrious annals have we its members been confronted with so many issues basic to the future of our profession and to our field of specialization. It is, therefore, with more than usual humility that I seek for words with which to thank you for giving to me for this brief moment the ultimate honor in American Surgery, and to signify my sense of lacking those qualities so needed in times of change, urgency and crisis.

For two years and a half our nation, with its allies, has been engaged in war, a struggle to the death against barbaric and brutal forces of darkness. The ferocity and enormity of it have torn deeply into the structure of civilization and into our lives, and have destroyed most of our peace time plans and visions. Every member of our Association has taken a part either in the planning on the home front or in active prosecution of the conflict in the Armed Forces, to the limit of his strength and ability. The time is not yet when we can summarize and evaluate these efforts, but let us express now our admiration and appreciation of the many from the Association and from our profession who have been and are now so ably and unselfishly carrying on the high purpose of medicine on active service with our Armed Forces over all seas and on all lands.

I am sure we have all wondered at times in the past year what more we should be doing to maintain the standards for which we have long struggled.

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\* Delivered before the American Surgical Association, May 3, 1944, Chicago, Ill

and how best we might direct our activities to keep abreast of, and if possible to lead, the changes that are taking place in the shifting relations of medicine to our social structure. Since these changes carry an implied challenge to our past performance and veil the future with uncertainties it has seemed to make it important to bring before you now some of the issues that present themselves to us as individuals and as members of the Association, therefore, I shall limit myself to a simple recital of those that seem most pertinent to Surgery at this time. Of necessity, I must repeat many of the points emphasized in the Presidential addresses of my recent predecessors, notably those of Arthur Dean Bevan, Dallas Phemister, Vernon David and Evarts Graham in his reincarnation of Founder Gross. The purpose of the Association is in general known to all of us, but lest we forget let me repeat from the Constitution "The object of this Association shall be the cultivation and improvement of the science and art of surgery, the elevation of the medical profession and such other matters as may come legitimately within its sphere." This is the broad view, one that we have at times forgotten and represents a goal toward which we should constantly reorient ourselves.

#### RELATIONS TO THE SOCIAL STRUCTURE

The relations of the medical profession to the social structure of our country have been under discussion for years, the threat of change becoming more and more acute. Whether the free competitive type of practice under which we have grown up shall in part or wholly be replaced by a controlled and subsidized method of caring for the sick is a possibility that confronts us. Many forms of cooperative practice have been suggested and there seems little doubt but that the profound social and economic conditions that will follow the war will result in significant and perhaps revolutionary changes in medical practice. It is not timely to elaborate here upon plans for future medical care, but one may state that thus far in the face of threatened change, the leaders of medicine have spoken at times in muted voice and in feeble tone. We can only hope that medicine will provide statesmen of sufficient stature to direct these movements into the high levels toward which we have striven during the time when medicine was under the dominance of the individual. As an association, perhaps we do not wish to attempt participation in such leadership, but whether we wish it or not we have a duty and an important interest in safeguarding our ideals of surgical practice if there come changes in the established methods of caring for those who are ill. At present there are forces working to remould Medicine through the more or less violent actions and reactions of pressure groups. The future health of the nation is worthy of greater consideration and if ever it be managed with an appreciation of its worth, it would demand a Minister of Health in the Cabinet with competent advisors from the laity and the profession who together could work out in an orderly fashion a plan that would be for the betterment of all. A statesman has said "The health of the people is the first concern of government", and we can

rightly insist that it be given statesmanlike consideration rather than that it be determined by political expediency

#### RELATION TO MEDICAL EDUCATION

Under the stern necessity of war there have come almost unbelievable changes in medical education the pattern of which has been so slowly and painfully developed in the past thirty years. The selection of students for entrance to Medicine is now in part in the hands of the representatives of the Army and the Navy. Premedical training is shortened and its content changed, while the medical course itself is accelerated to a continuous performance. We are all heartily agreed with these or with any courses that will win the war and safeguard the health of our fighting men but we must realize that these changes are those of expediency and that they will give birth to vexing problems in the future. A study of medical education at this time discloses a self-confessed deterioration of instruction in many schools with the possibility of a serious breakdown in most, if there occur further depletion of faculties, lowering of educational requirements, or a let-down in the personnel qualifications of trainees assigned to medical schools. Graduate Training worthy of the name has ceased. The present G-9-G program is a distinct aid in caring for sick and injured civilians, but contributes little to what we have come to consider true Graduate Education. In the endeavor to spread the intern crop as widely as possible to help out the home front, many men are forced to accept internships in hospitals where training is virtually absent or present only in what might be described as a trace in preparation for their career in the Army and the Navy. This means that after the war there will be from 20,000 to 30,000 young men who will have had educational opportunities of a character inferior to those offered in the prewar period.

It is true that in many instances the training and experiences gained in Service will compensate in part or wholly for these deficiencies. There is no doubt but that the discipline, necessity for independent decision and habit of cooperative action acquired on active service, develop many admirable traits better than do any other school. However, many of these young men will demand further training of the orthodox variety after hostilities cease.

This task falls directly on the shoulders of those of us who have remained at home and the manner in which we carry it out will importantly determine the character of surgical service rendered to this country for the next generation. There has been set up from our profession a committee for Post-War Planning for Medical Services with representatives from the American Medical Association, the American College of Surgeons, and the American College of Physicians and the Army, Navy, Public Health Service and the Veterans Facility which is working to prepare to fill the needs and wishes of the demobilized medical officers. In order to get some idea of what the medical officers now in Service will want after demobilization, a ques-

tionnaire will be sent to every medical reserve officer on active duty. It is hoped that these returns will clarify to some extent the problems that face us. A subcommittee is now active in studying the question of providing Graduate Training in the medical and surgical specialties for those whose training has been interrupted or never started because of service with our Armed Forces. Feeling that the members of this Association should have the opportunity and would have the will to direct these efforts to enlarge and improve schemes for advanced training in surgery and its specialties, a committee was appointed in November with the sanction of your Council, to explore the field and to seek advice and help from every member of the Association. This committee will work with the main committee for Post-War Planning and carry your thoughts and aid to it. While no one can predict with accuracy what the needs of the future will be, we can plan to meet certain demands that inevitably will be made on our clinics, hospitals and schools. Judging from personal correspondence with men on Active Service, their desires for further training in Surgery will cause them to fall into several well defined categories.

*First* Many well trained men will want refresher courses designed to refamiliarize them with those phases of civil surgery not seen in military experience. The demand will be not only on the clinic but also on the laboratories of the basic medical sciences.

*Second* A larger group will comprise those men who have had an internship or a short residency who will seek training that will prepare them to take the Specialty Board Examination. This offers many delicate and difficult problems to us and to the Boards. By and large, the Boards will give credit for one year spent in military service with credit beyond that time given only after a careful evaluation of work actually done. We must provide opportunity not only for those whose training has been held up by the war but we have a duty as well to the on-coming medical graduates, and those worthy of advanced training in both classes should receive it. In order to accomplish this objective we will have to increase the number of available residencies, by increasing the number of hospitals where such training is available and by temporarily at least enlarging the number of residencies in those hospitals where acceptable training is now offered. The American College of Surgeons is committed to a greatly enhanced effort to stimulate and aid hospitals in setting up new schools of Graduate Training and there is no doubt but that the number of hospitals giving adequate training will be materially increased. In the past, there has been the greatest divergence in the methods used in carrying on advanced training in the hospitals of this country. Most frequently it has been effected by precept, in the ward and the operating room. Its greatest weakness has been in the lack of a proper integration of the clinical and basic medical sciences. A rescrutiny of our methods of training with the addition to it of more opportunities for study of anatomy, pathology, physiology and chemistry in relation to clinical problems would enable us to offer our residents better training at more

truly university levels and would enlarge the number of those to whom such training could be offered. In short, the stimulus of meeting the challenge of this emergency may well be the opportunity to reorganize and improve the quality of our Graduate Teaching.

In the past the opportunities for Graduate Training have been offered to a carefully selected group and many of the men who now will want advanced training would not have qualified for it in the ordinary course of events. It is natural that one will be influenced in choosing a resident by a man's Service record, but this alone is not enough, in addition he must be competent and intellectually worthy of this training. I do not know how best to select men from this great group for Fellowship and residencies, except that each of us will instinctively use the old yardsticks that we have found satisfactory in the past, and we should not be satisfied with short measure since, after all, our responsibility is to the American people of the future as well as to aspirants of today.

Residencies and Fellowships require money, and while the government may offer financial support to veterans for vocational training, we would be well advised also to plan to meet these needs from other sources. Residents are essential to the proper functioning of a hospital, yet, in the past hospitals have been willing to pay everyone on the staff except the physicians in training. There is every reason why hospitals should support residents who not only improve the care of the patient but make up their staff in the future. We should not only seek for funds with which to carry additional residents but we should increase their stipend to a level of financial decency. Hospitals, Medical Schools, Foundations, private individuals all should be approached for the money to carry forward this training program so vital to the health of the nation for the next two decades. If every member of this Association, who is not in the Armed Forces supported a Fellowship for three years, it would be a minor financial burden to us and would give training to 200 men. If we put our minds to it, the financial difficulties could largely be settled within the resources of our own communities.

A third group, a much smaller one, should be borne in mind, that is, those men qualified to do and desirous of carrying on research. We should have laboratories and financial support ready for them on their return. It is imperative that opportunities for investigation be given every young man who wishes to do research, as after this war the torch of science will still be burning in only a few spots on the earth. After the war only Russia and Great Britain, of the great European nations, will be able to foster scientific investigations and they will be carrying in addition a tremendous load in reconstruction and readjustment. Following the destruction caused by years of heroic and bitter war, China will be obliged to start her schools from scratch and will look to us for aid in training those who will care for the health of her enormous population and rebuild and develop her medical centers. South America will want even closer intellectual association with our schools and clinics, in the face of the weakness or absence of the

European medical centers with which they formerly were associated. The thought of these responsibilities is a staggering one, but if dwelled upon will serve to bring home to us the importance of planning and preparation for post-war graduate study and research not only for our own but for a large part of the world.

#### SPECIALISM

We as an Association are vitally interested in every phase of surgical evolution. Since our organization in 1880, there have been many changes in surgical practice brought about by the rapid development of knowledge and technics. The increase of specialism has more than kept pace with the speed of our intellectual art itself but its earlier manifestations were sporadic and without continuity. It was not until surgery itself began to advance after the conquest of pain and sepsis in 1846 and 1867 that specialization, as we know it today, had its origin. The founder of our Association, Samuel D. Gross, stated in 1876 that "It is safe to say that there is not a medical man on this continent who devotes himself exclusively to the practice of surgery and that American medical men are general practitioners and cover the entire field of medicine, surgery and obstetrics." At the present time approximately 50,000 men in the United States specialize and at least 25,000 limit themselves to practice in some one field. There are now twelve special departments of surgery, all of them except obstetrics and gynecology have had their origin in what we call general surgery. These surgical specialties were originally created by general surgeons who because of opportunity or interest devoted their main efforts to one phase of their art. True specialization is a striving for perfection and we owe a great debt to those who have by their efforts in limited fields so greatly enhanced our knowledge of the whole. At the time when our system of medical education was so radically reorganized and put on its present basis, commercial specialism based solely on a desire for income, and justified by a two weeks course in Vienna, was a threat to honest specialization, a menace to the public, and a shame to our profession. In the time that has passed since then, through our own efforts, expanded through the Colleges and Boards, we have put the requirements for specialization on a high plane. Granting that special study and perfection of technics in a chosen field have increased our knowledge and skill, the establishment of rigid lines of separation from the parent stem offers dangers for the future. To quote Victor Bonney "Whereas before their advent, the surgeon made the specialty, it is now possible for the specialty to make the surgeon." A specialty justifies itself only so long as it advances the border lines of knowledge in its field, because of intensive application to it or because it develops the technic peculiar to that field to a high degree. To carry on a specialty on the latter grounds is a convenience to the surgeon and may benefit the patient, but as a basis for training succeeding generations it presents many dangers since technics may become dominant while the fundamentals of surgery are neglected. When

a specialty becomes static and the aspirant in that field is trained solely in the specialty, he will tend to become a mere technician, with a limited usefulness and a narrow vision. If the process continues, his successors trained by him, in turn, will fall heir to progressive limitations. We will all agree that better surgical work is done in any field if one concentrates one's efforts on that objective, on condition that one is well founded and informed on surgery as a whole. Specialization is necessary and desirable but only if it continues along the broad path in which it had its origin. As a matter of fact we all are specialists, since each of us has his own particular field of talent. These aptitudes are developed by our own interest or forced upon us by chance, opportunity, or by some paper or book we have written. I often wonder, what is a general surgeon? The most one can say is that those of us who call ourselves general surgeons take pride in believing that we look upon the body as a whole and exhibit an interest in studying its responses to abnormal conditions of disease. In addition we may be known for our dexterity in thyroidectomy, colectomy, gastrectomy or pneumonectomy. These are our specialties, and of course many men who call themselves specialists would, under this concept, qualify as general surgeons. But if we all indulge in specialism to some degree, we all must admit the necessity of a broad training in the fundamentals before limiting our efforts to one phase of the art. What we should strive for is not to make everyone a general surgeon, but to make all who practice in any surgical field, Generals in Surgery. The thoughtful men in all fields of surgical endeavor admit the necessity of close integration and cohesion between fundamental and special training. One year ago Vernon David brought this matter to your attention and appointed a committee to explore the possibilities of a basic examination in Surgery for all aspirants to surgical practice of any type. In General Medicine, such a basic examination in the broad principles of medicine is given, and is a requirement for the candidate before he can seek certification as a specialist. Unfortunately in Surgery, there has not been the same coordinated development of standards for certification due in some part to the long past reluctance of members of this association, either to recognize the need for standards or to aid in their establishment. Consequently, standardization of surgical practice in this country has developed from many roots. The American College of Surgeons was formed in 1912, and first setup requirements for admission to Fellowship. At that time graduate training in surgery and its specialties was practically nonexistent except through the apprentice system. The task of passing upon the capability of those doing surgery in a great nation, in places varying in size from cities with millions to villages with but hundreds, was a difficult one and impossible of accurate achievement. One cannot, however, overestimate the importance of the event although this is often overlooked by those who criticize the College for accepting Fellows who were deemed unworthy. The difficulty lay in a complete absence of accurate yardsticks of excellence and in the struggle to reconcile practice in city and in country. The American College of Surgeons not only attempted



to designate the skillful in practice, but it improved the tools with which the surgeon worked. Through the standardization of hospitals, it provided the surgeon with an environment in which he could have every facility and in which the well-being of the patient was safeguarded. Through its committee on Graduate Training, it has aided hospitals in developing facilities for advanced education and has consistently urged that these facilities move toward higher educational levels. As time went by, standards for educational requirements for admission to Fellowship were raised slowly, but one may prophesy surely, in the attempt to include and reconcile the different types of practice in town and city.

In the meantime the Surgical Boards were organized, by which higher standards were set. The Board of Ophthalmology was organized in 1916. Later there came Boards in Otolaryngology, Obstetrics and Gynecology, Dermatology and Syphilology, and, in 1933, the American Medical Association authorized the Council of Medical Education and Hospitals to formulate standards of administration for Boards to be based upon the form of those already established. There are now fifteen Boards, nine of which are related in some degree to Surgery. The American Board of Surgery organized at the initiative of this Association came into active being in 1937 and has had an outstanding record of influence and stimulation. Thus through a series of historical accidents, one may become certified as a surgeon by passing through any one of the nine portals of the Boards or under the arch of the College. We cannot turn back the clock and we must admit that both the Boards and the College fulfill important functions and should be given our cordial support. It is regrettable that so many ways of reaching the heights have been hewn but in the last analysis this redundancy of effort has been due to the rapid development of surgery and its specialties and to the pride of the specialist in making his own path to his own particular field. One may well ask, would it not be to the best interests of surgery to coordinate and amalgamate in some way the standards of that Art? All of the Boards require a knowledge of the Basic Sciences in relation to health and disease, and everyone will admit that this knowledge is fundamental to everyone worthy of the title Surgeon no matter what his specialty may be. Could not there be developed a basic examination in surgical fundamentals that would be taken by all those wishing to become candidates for the Boards and for Fellowship in the American College of Surgeons? Passing such an examination would be a preliminary to later taking the Final Examination of the Specialty Boards and would admit the successful candidate to Junior Membership in the American College of Surgeons. Such a system would anchor firmly the specialists in the parent Art and Science and would bring together the various now divergent agencies that have a common cause, that is, the advancement of Surgical Practice and Service. These ideas have been discussed by the members of your committee and will be reported to you through the Chairman, Doctor Whipple. Meetings have been held with a similar committee from the American College

of Surgeons, Board of Orthopedic Surgery and the American Board of Surgery. It is hoped that some progress has been made in bringing about a cohesion in surgery that, if finally effected, will restore us to a state so that we may strive together towards a common goal. All of us must study this possibility and if, finally, it is deemed advantageous action may come.

Tradition and custom have decreed that the American Surgical Association shall remain a comparatively small organization but they likewise insist that we constitute a Forum in which the new advances in Surgery shall be presented each year. It is a question whether the two are longer compatible. You are familiar with the facts concerning our development, as they have frequently been presented to you. The year the Association was formed, the membership was set at 150, and the population of the country was 50 million. At that time, there were few specialists and it was a rarity for anyone to limit his work to surgery. In 1939 the membership was raised to 175 and the active membership has been increased slightly by lowering the retiring age to Senior Membership, and young men, not members of the Association, have been allowed the privilege of presenting papers if they are sponsored by a member. These changes have been helpful but they have not adequately solved the difficulties. We have admitted the necessity of having as members those in Surgical Specialties who are adding knowledge and conducting research in their chosen fields. We value the membership of these men and our programs have gained in breadth and interest by their contributions, but there is reason to believe that we would profit by a still wider representation of leaders in the specialties in our membership.

In considering the size and sphere of activity of the Association, we have apparently neglected to take into account our greatest contribution. Graduate Training in Surgery is largely a development since 1920 and has done more to stimulate original scientific work in surgery in this country than has any other force. A large part of the advance in surgery in the past 20 years has been due to the efforts of these young men in our laboratories and clinics, and a familiarity with surgical literature or an acquaintanceship with the younger group as they have come up for examination by Surgical Boards, impresses one with their superlative ability and their potentialities for leadership. Certainly everyone who passes a Surgery Board is not automatically a candidate for membership in the Association, but we must recognize the fruit of our Graduate Training Program and realize that never before in our history have we had so many capable young men engaged in forwarding surgical knowledge from whom we could profitably select new members. We should learn of their work at first hand and if we do not give them opportunity here they will develop societies of their own and leadership will drift from us. Most of them are now engaged in caring for the wounded, but many of them are worthy of our consideration and we should look forward to their incorporation into the Association when they return. If the Association is to maintain its proud place and live up

to its original tenets, we must recognize the almost unbelievable changes that have taken place in the personnel of our ranks due to our own efforts at bringing training in Surgery to higher educational levels. The population of the country is now nearly trebled since the initiation of our organization, approximately 20,000 men in this country limit their work to general surgery alone. Our American Board of Surgery has certified 3000 men and other Surgical Boards have certified more than this number. Surely to get the best from these, we could well consider some enlargement of our membership. During the next few years there will be available only a comparatively few vacancies for membership due to the passage of a like number of our members of the 60 mark. As we stand now, only one other force may increase this number, but let us hope it will operate feebly, or not at all.

Whether our membership is inclusive enough to represent major surgical progress in teaching, research and in the clinic, we can leave for the moment. Do we now give opportunity to all of our members who wish to present their work and ideas? Even since I have been a member there have been many papers read by title, often the number thus offered has been nearly as large as those read on the floor. While we admit the difficulties and sincerity of the hard working program committee, many of our members have been piqued at having a paper over which they have slaved, thus presented by a sentence. At times resentment has been felt by those who did not get on the program and the apprehension of being passed by has often acted as a deterrent to further efforts. If this feeling could be removed, it is more than likely that the number of papers submitted would immediately be doubled. It would indeed be the rare paper submitted by any one of our members that would not be worthy of the audience.

In order to give opportunity for presentation of a larger number of papers, some adjustment of present practice would be necessary. The first meetings of the Association were held for three days, in fact our By-Laws read that "The meeting shall continue for three days, unless otherwise ordered by a majority vote." Some time in the historical past the meetings dwindled by half a day and this year, as a war measure, perhaps with the fear that there would not be material enough to run the course, it was reduced to two days. Suggestions have been made many times that we could increase the number of papers read by allowing ten minutes for their reading. The possibility of having sections running simultaneously on papers of like interest has also been mentioned. Under our present system, discussion is often more limited than is the demand for it. Certainly every effort should be made to stimulate our members to present their work and to make each one feel clearly that his productions are solicited and welcomed. This problem of enlarging the program is one for study and I hope that the appointment of a committee will be authorized to make such recommendation as will enable an enlarged and more completely representative program to be offered at our future meetings.

The question of enlarging the membership in the Association is one that

has been much debated and one that is answered in divergent manner by our members. There must be a membership that would represent our maximal efficiency to carry out the avowed aims of the Association. This problem has been the subject of study and might profitably become so again because of the accelerated tempo of scientific progress. In the meantime, confronted as we are with so few vacancies in our ranks and with the many brilliant young men in all fields of surgical activity who could add to our prestige, might we not consider again the advisability of a modest enlargement now. It is five years since the membership was increased by 25. This increase has been well digested. I suggest that, in addition to filling the vacancies that occur each year we add for the next five years five men each year. This would increase our active membership to 200 in that time, certainly not a number larger than would contain the outstanding contributors to surgery in this country and Canada. I believe that without some increase at this time we cannot remain truly representative and that this enlargement will greatly strengthen the Association. If the problem is studied, as it should be and further changes seem advisable, they can be readily effected at any time by a vote of this body.

In conclusion, I would like again to pay tribute to the members of our Association and to the thousands of young men who are caring for the sick and wounded on the battle front. They have earned our deepest gratitude and their work merits our highest admiration. We read with pride the reports that come from the Surgeon-Generals of the Army and Navy in which are emphasized the vast improvement in the surgical care of our injured soldiers and sailors over those of previous wars. The public press ascribes this great advance as due to some product of laboratory ingenuity, such as plasma, sulfa, and penicillin. These are mere adjuvants that will eventually be replaced by better things, but the public likes to glorify the gadget.

The truth is that the health of our Armed Forces and those of our allies is being guarded by the best trained, most capable medical officers ever to serve with any armies in the history of war. They are giving a vital and vivid demonstration of the worth of the methods of teaching and training developed since the last war. The modern miracles of medicine and surgery are due to the men who perform them not to any minutiae of their techniques. For their skill and devotion we acclaim them, taking pride in the fact that in some part at least, we have set the goal that they have reached. The future of Medicine and Surgery will be brilliant in their hands, in the present it is our task to prepare the way for their home-coming in such fashion that standards of training and achievement will be maintained and that the American Surgical Association will continue to hold the high part in Surgical leadership it long since assumed in the past.

*Described by Brigadier General Rankin as "one of the finest dissertations on management of wounds which has been submitted through the Office of the Surgeon General of the U S Army," this paper by Colonel Churchill, arrived just as we were closing the first issue of the ANNALS OF SURGERY devoted to the transactions of the American Surgical Association. It was immediately accepted to appear in the Annals with the Transactions as a contribution by Col Churchill, in absentia. The Editors join the Association in welcoming this fine report from an important battle area, and in congratulating Col Churchill for his high accomplishment in the field and in reporting such excellent work.*

## THE SURGICAL MANAGEMENT OF THE WOUNDED IN THE MEDITERRANEAN THEATER AT THE TIME OF THE FALL OF ROME

COLONEL EDWARD D CHURCHILL, M C , A U S

*"I would remind you again how large and various was the experience of the battlefield, and how fertile the blood of warriors in rearing good surgeons"*

T CLIFFORD ALLBUTT

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### FOREWORD

BY

BRIG GEN'L FRED W RANKIN, M C

DIRECTOR SURGERY DIVISION U S ARMY

*The present-day health standards of our troops and survival rate among our wounded have been unequalled in the history of warfare. Perhaps one of the most important factors contributing to this highly gratifying record has been the role played by the professional consultants whose functions may be broadly described as administrative, correlative, advisory, educational and analytical. Consultants in the major fields of endeavor have been attached to every Service Command in the Zone of Interior and to all active Theaters of Operations. Selected on the basis of their special training and extensive background and on their eminent qualifications, they have been able to perform an incalculably valuable function in promoting higher standards of medical practice in this war.*

*As Surgical Consultant to the North African and Mediterranean Theater of Operations and representative of this group, Colonel Churchill has done more than improve the quality of surgery performed in this Theater. Uniquely equipped to perform his mission and imbued with the true scientific spirit, he early recognized the inadequacy of certain preformed concepts in the surgical management of the wounded. With this flexibility of mind and with an elastic organization, he has utilized an investigative approach and drawn*

*upon battlefield experience to evolve more rational and effective methods in the surgical care of the wounded. In this article, he has epitomized these observations and principles which constitute not only a contribution to war surgery but also to the advancement of medical science.*

WOUND MANAGEMENT may be divided into three phases—initial, reparative and reconstructive. The first two are concerns of an overseas theater. The latter is the mission of the Zone of the Interior.

#### INITIAL SURGERY

The initial surgery of the forward area is primarily directed toward the preservation of life and limb. The immediate physiologic disturbances incident to blood loss and the wound itself are corrected by both resuscitative and surgical measures. Wound infection is prevented or controlled by surgery and chemotherapy.

Resuscitation from shock has two goals: first, to render the casualty transportable and preserve his life until a hospital can be reached, and second, to prepare the casualty to withstand life saving surgical procedures. Shock as observed in the forward area is caused by whole blood loss except in burns, crushing injuries or rapidly advancing infection. Plasma is used in the divisional area to prepare the wounded for transportation and keep them alive until they can reach a hospital. Whole blood would be preferable, but it is not practical to use transfusions within the divisional area.

Plasma alone is not adequate to prepare a seriously wounded casualty to withstand the surgical procedures that are essential, or to carry him through the critical postoperative period. After admission to hospital a limited amount is used to augment the effects of whole blood transfusion. Plasma is a substitute for whole blood only in the sense that it can be packaged and stored in adequate quantity in areas where blood cannot be obtained. Plasma is not a substitute for whole blood in the physiologic sense. For these reasons a Blood Transfusion Unit procures and processes whole blood in the base and distributes it to the Army installations.

Shipments of blood were made by LST to the Anzio beachhead in February. As the front advanced and forward landing strips were opened, blood has been shipped each day by plane. In approximately four months, over 16,000 pints of whole blood have been drawn and processed for delivery to the Fifth Army. The blood is drawn by vacuum into bottles that are used only once. Glucose is added to the citrate as a preservative. Each flask of blood is triply checked for type, examined by smear for malaria and Kahn-tested.

Although Type "O" blood is commonly referred to as "universal donor" blood, its use in large amounts in patients of other types is hazardous unless the agglutinin titer is low. Every bottle of blood is titered and only those with an agglutinin titer less than 1 to 64 are issued as "universal donor" blood. All banked blood carries an expiration date of seven days.

To augment the supply of blood forwarded from the base, evacuation hospitals maintain their own unit blood banks. Responsibility for the supply of type specific blood other than "O" rests upon the individual hospital.

The initial wound operation is directed toward the prevention of infection by a complete excision of tissue devitalized by the missile. Procedures such as closure of a sucking wound of the chest or suture of a perforation of a hollow viscus restore physiologic equilibrium as well as arrest the dangers of infection. Recognition of all devitalized tissue is often times impossible, particularly in a massive wound or one complicated by skeletal injury. Disturbances of blood supply and subtle changes that indicate impending death of tissues may not be detectable. In a certain number of these cases mixed anaerobic infection of residual dead tissues is the inevitable sequela. Others will develop invasive infection spreading from the wound to involve normal tissues. To minimize the incidence and hazards of infection, primary closure by suture is strictly avoided. Exact maintenance of the reduction of fractures by precise methods is precluded by the necessity for evacuation to the rear, so temporary or transportation splinting, usually with plaster of paris, is employed.

Chemotherapy is initiated in the field by local and oral administration of sulfonamides. The value of this procedure is questioned by many surgeons of experience. Preoperative penicillin therapy is started on all but the lightly wounded casualties on admission to hospital in the forward area. At operation, topical application of penicillin is carried out only in wounds penetrating the meninges, serous cavities and joints. Parenteral administration is continued beyond the period of the likelihood of infection or until established infection has been controlled. No patient is held in the forward area solely for the purpose of continuing penicillin therapy.

Just as plasma is not a substitute for whole blood in resuscitation, neither are sulfonamides and penicillin substitutes for the surgical excision of devitalized tissue. Chemotherapeutic agents cannot sterilize dead, devitalized or avascular tissues nor do they prevent the septic decomposition of contaminated blood clot.

In this war there have been two quite different approaches to the application of chemotherapeutic agents to military surgery. The first would utilize these agents to permit delay in wound surgery, and minimize the completeness of the excision of dead tissue. The second employs chemotherapy to extend the scope of surgery and achieve a perfection in results previously considered impossible. The latter policy has guided the surgery of the Mediterranean Theater. To reiterate the axiom that penicillin is not a substitute for surgery is not enough. Every surgeon must learn that chemotherapy opens new and startling possibilities in wound management.

The magnitude of the surgical problems that confront the forward surgeons when supported by adequate resuscitation therapy is difficult to visualize by one not having a first-hand acquaintance with their work. Highest standards of precision must be maintained if the potentialities of surgery

are to be realized to full advantage. This precision must be attained in the use of the adjuncts to surgery as well as in operative techniques. Initial surgery cannot be carried on as a hasty, slap-dash and bloody spectacle, with rapid evacuation of the patient to the rear if satisfactory results are to be achieved. The average operating times for certain types of cases recorded at an evacuation hospital were one hour 49 minutes for penetrating wounds of the head, two hours for wounds of the abdomen, two hours and a half for wounds of the thorax. Many casualties have multiple wounds that require several major procedures in sequence or simultaneously. Postoperative care is as important as the operation and may demand holding the patient for ten days or longer.

Triage at the divisional clearing station based on the urgency of the wound and the condition of the casualty establishes a "three-point forward system," as described by Jolly in the Spanish Civil War. This provides a small surgical hospital for first priority casualties—in this theater a single platoon of a field hospital reorganized and equipped for this specific mission. Other casualties of less urgent types are transferred back to the chain of Evacuation Hospitals. An important modification of the system has placed the Field Hospital Platoon in physical conjunction with the clearing station triage point. This provides for the immediate transfer of wounded from the clearing station to the first priority surgical hospital by hand litter. No pause is required for resuscitation or interference with splinting or dressings. Expert surgical management that embraces resuscitation, operation and prolonged postoperative care, becomes immediately available. Cases with a continuing source of shock that cannot be made transportable without an operation are thus salvaged and the desperately wounded receive expert care as far forward as it can be provided.

Surgeons assigned the responsibility of caring for the wounded in a first priority surgical hospital must be highly trained and experienced, as their tasks are the most exacting of military surgery. The Auxiliary Surgical Group has been found ideal as a source for this personnel. The experience of the individual surgeon is augmented in the base during periods of an inactive front. Unity and uniformity in the control of this portion of forward surgical personnel has produced a high level of competence as well as economy in the deployment of specialized surgical skill and talent. If the achievements of surgery in this theater are ever judged noteworthy, they are attributable to the fact that expert rather than inexperienced surgeons are doing the work. All other measures are ancillary items.

A well-run first priority surgical hospital exerts a remarkably favorable effect on the morale of combat troops and their officers. The divisional medical service receives a stimulus to maintain its arduous task by first hand evidence that the lives of the most desperately wounded may be saved by skillful first-aid measures and rapid evacuation. Splinting is improved, the use of plasma in Aid Stations is increased and the temptation for clearing



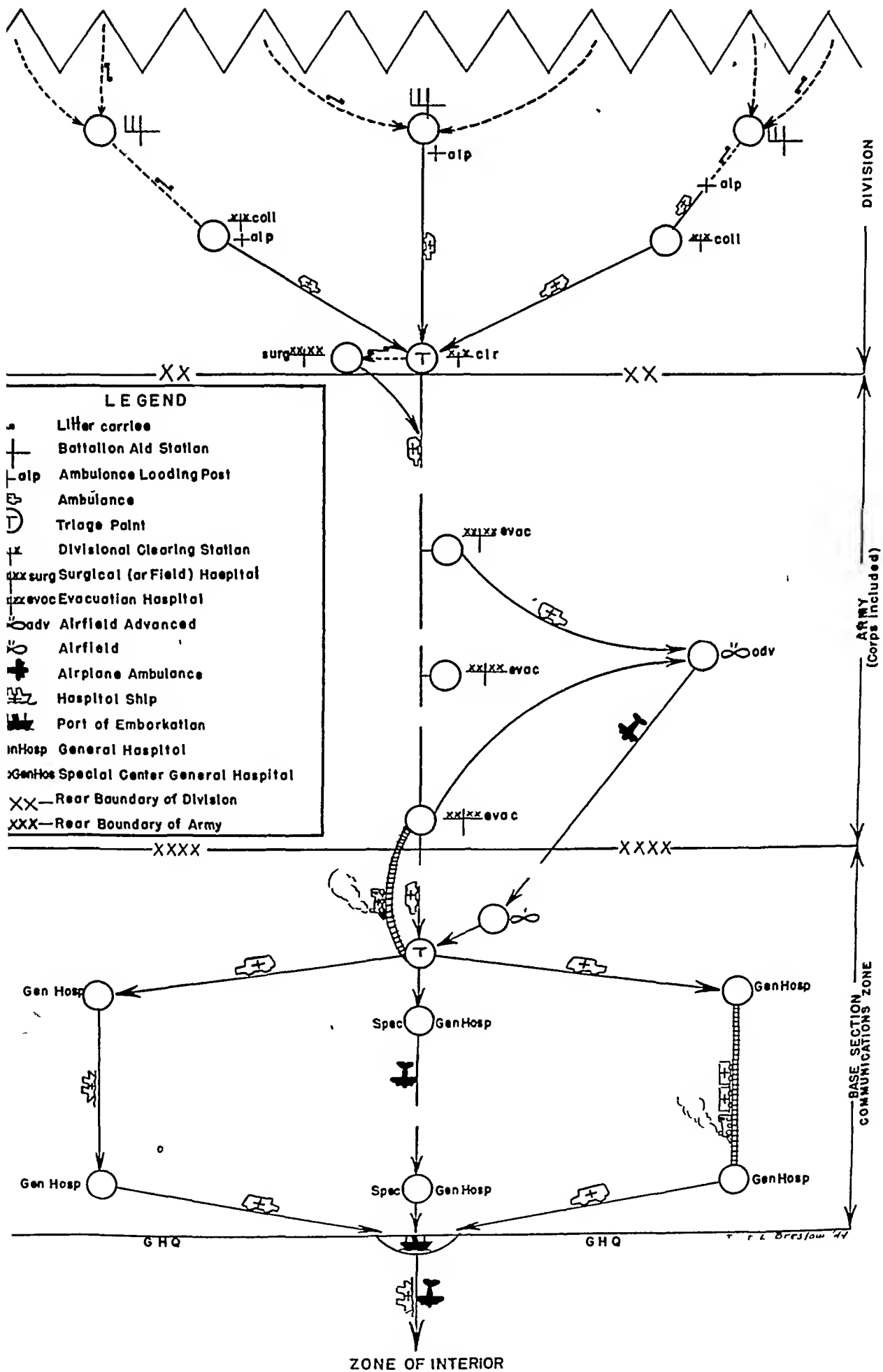


FIG 1—Diagrammatic representation of an Overseas Theater

or collecting companies to indulge in heroic surgical procedures for which they were never designed or equipped is removed

Evacuation hospitals handle the great bulk of the wounded in the forward area, as the small group of first priority cases diverted to the Field Hospital Platoon constitutes approximately one-thirtieth of the total number. These institutions, with trained and experienced professional staffs, have attained a high degree of proficiency in the procedures of initial wound management and remain the backbone of the Army medical service

#### REPARATIVE SURGERY

A highly significant and far-reaching advance in military surgery has taken place in the base hospitals with the development of what may be called *reparative surgery*. Wounds left unsutured at the initial operation are routinely closed by suture, usually at the time of the first dressing. With the use of penicillin as a safeguard against infection, the management of wounds complicated by fracture or joint involvement has been revolutionized. Surgical procedures in special fields of surgery—thoracic, craniocerebral, abdominal—have also been radically altered by the application of similar principles. The significance of this development and its effect on returning an increased number of wounded soldiers to duty and in preventing deformity, disability and death in the seriously wounded can hardly be overestimated.

Reparative surgery is not to be confused with the reconstructive surgery of the Zone of the Interior. Reparative surgery is designed to prevent or cut short wound infection either before it is established or at the period of its inception. Once established, wound infection is destructive of tissue and at times of life. In many instances it permanently precludes the restoration of function by the most skillful reconstructive efforts.

If the initial wound operation has been a complete one, wounds of the soft parts may be closed by suture on or after the fourth day. The dressing applied in the evacuation hospital is removed under aseptic precautions in an operating room of a general hospital at the base. Following closure, the part is immobilized preferably by a light plaster encasement, or if this is impractical, by bed rest.

Decision to close a wound by suture is based solely on an appraisal of the gross appearance at the time of removal of the dressing. Preliminary qualitative or quantitative bacteriologic analysis of the flora of the wound by smear or culture does not provide information pertinent to this decision or allow the prediction of the result. "Clean" wounds that heal by first intention after delayed closure may show a profuse and varied flora, both anaerobic and aerobic. Identification of species and tests for pathogenicity would require weeks of arduous laboratory procedure.

It is estimated that during the Italian Campaign alone, at least 25,000 soft-part wounds have been closed on the basis of gross appearance only. Healing has resulted in approximately 95 per cent, and no loss of life or limb or serious complications have been reported. Residual dead tissue in a

deep recess of the wound is the most common cause of the failure in the 5 per cent that may be classed as unsuccessful closures. If the suture is not successful because of infection, appropriate studies and corrective therapy is instituted before resuture is attempted.

The presence of residual dead tissue or established invasive infection at the time of the first dressing is evidenced by discharge of pus and redness



FIG 2—Platoon of a Field Hospital acting as a forward surgical hospital with Fifth Army in Italy

and edema of the wound margins. When these are present but minimal, the wound is allowed to "clean up" with moist dressings. Surgical excision of devitalized fragments or removal of retained foreign bodies may speed this process. Secondary closure may then be performed after a few days. If established infection is severe, or if the patient is toxic or anemic, a course of



FIG 3—Initial wound surgery for first priority cases at the rear boundary of the divisional area  
Surgical team operating in a Field Hospital Platoon





FIG 5—Evacuation Hospital with 11th Army in Italy—December, 1943

FIG 6A

FIG 6B

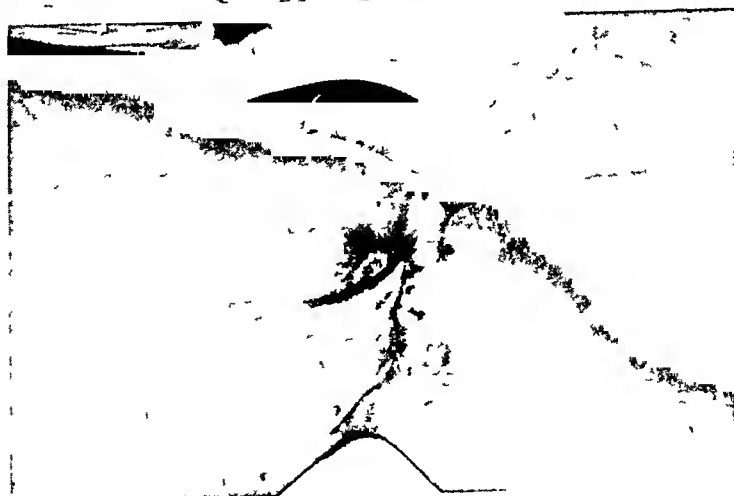


FIG 6C

FIG 6—Reparative surgery of soft part wound of axilla

(A) First dressing at base hospital four days following initial debridement in forward evacuation hospital

(B) Closure of wound by secondary suture with advancement of skin flap into axilla

(C) First intention healing 12 days after suture, 16 days after wounding



FIG 7A

FIG 7—Reparative surgery of wounds compounding fractures of both bones of the forearm and fracture dislocation of the humerus

(A) First dressing at base hospital on fifth day Secondary anemia corrected by 1600 cc of whole blood Penicillin therapy

(B) Screw fixation of comminuted head of the humerus following open reduction of dislocation

(C) Reduction of fracture of both bones of the forearm with wiring at fracture site of the radius  
Application of skeletal traction

(D) Wound closure

(E) Postoperative skeletal traction



FIG 7B



FIG 7C



FIG 7D

penicillin therapy and blood transfusions is instituted and followed by radical wound revision with staged closure

The topical use of sulfonamides appears to contribute nothing to the favorable results of reparative wound surgery. Parallel series of closures show as satisfactory or better results without the topical application of sulfonamides at the time of suture, as with it. Penicillin therapy is entirely unnecessary as an adjunct to the usual reparative surgery of soft-part wounds. It is used parentally for cases of established infection and in the reparative surgery of complicated wounds.

The reparative surgery of complicated wounds including those with extensive muscle damage as well as those with skeletal or joint injury and penetration of the viscera, is a more major undertaking. It is in this group that both the incidence and hazards of infection may be expected to be greater. It is this group of cases that is kept on penicillin therapy during the interval between initial and reparative surgery and so maintained until the likelihood of infection is past. Immediate correction of secondary anemia on arrival at the base is an essential part of the program as the days are few during which the anemia from the initial blood loss may be projected into the anemia of chronic infection and indolent wound healing. The procedures of reparative surgery are frequently of great magnitude and the patients must be adequately supported by whole blood transfusions before, during and subsequent to operation.

Compound fractures are removed from transportation splints, the wound is revisioned for further removal of devitalized tissue, reduction of the fracture is secured and maintained by skeletal traction, internal fixation or other means as indicated. The original débridement incisions directly compounding the fracture site are closed by suture. Dependent stab wound drainage to the fracture site is usually established for a limited period of time.



FIG 7E



Open arthrotomy is carried out for impending or early joint infection. Devitalized cartilage and retained foreign bodies are removed and the joint space closed. In a few cases when serious trauma or early established infection has irreparably ruined the joint architecture, resection of the joint

FIG 8A



FIG 8B

FIG 8C

FIG 8D

FIG 8—Reparative surgery of compound fracture of the femur

- (A) Suspension for operative access at the first dressing on the sixth day following initial debridement in a forward hospital. Anemia corrected by transfusion, penicillin therapy.
- (B) Comminuted fracture as received at the base following evacuation to the rear in a hip spica encasement.
- (C) Revision of the fracture site, with removal of residual devitalized bone fragments.
- (D) Closure of debridement incisions, establishment of posterior dependent drainage, wire inserted for skeletal traction.

has been performed and satisfactory healing in a position of maximum usefulness achieved.

Radical management of massive organizing hemothorax by thoracotomy

## SURGICAL MANAGEMENT OF WOUNDED

evacuation of the clot and decortication of the lung has proved its effectiveness in returning soldiers to duty and appears to have diminished the incidence of empyema. The same procedure applied to established posttraumatic empyema with penicillin therapy as an adjunct, is followed by immediate healing with a fully expanded lung. It is no longer acceptable to hold that a patient with a penetrating chest wound is making satisfactory progress as long as empyema has not made itself manifest. The focus has been changed from



FIG 9—Reparative surgery of thoracic wounds. Five patients, all with severe mixed infection empyema of residual hemothorax following debridement of wounds of the chest in the forward area. Varying degrees of pulmonary collapse and fibro-purulent loculation of pleural space. Without preliminary drainage thoracotomy with decortication of the lung performed on 9th, 16th, 21st, 21st and 21st days after wounding. Penicillin therapy, parental and topical. Complete primary healing, with fully expanded lungs—ready for rehabilitation to duty status.

the management of posttraumatic pleural infection to the preservation of lung function. In the history of military surgery this will stand as one of the significant advances of World War II.

Early closure of small intestinal fistulae is a life-saving measure. Repair of exteriorized segments of large bowel returns a certain number of soldiers to limited duty and simplifies the nursing problems of the evacuation of others to the Zone of the Interior. Loop-sigmoid colostomy as an adjunct to the management of wounds of the perineum and anal regions has permitted early secondary suture followed by closure of the colostomy and return to full duty.

Skin loss in wounds comes from the missile, the over enthusiastic surgeon or infection. Skin defects attributable to tangential hits or the tearing action of the missile at the wound of exit are repaired by skin grafts as early as the

fourth day following injury. In facial injuries, splinting of the bony parts and primary suture of soft parts with provision for drainage at the time of initial surgery is followed by meticulous wound management on arrival at the base. It is believed that there is a material reduction in the incidence of disfiguring mutilations. Extensive loss of skin and soft parts attributable to the missile is not commonly observed, and it seems likely that many of the facial mutilations of warfare are attributable to loss of tissue by sepsis and contracture—both preventable.



FIG 10—Tangential wound of calf producing skin and soft part defect measuring four by five inches. Secondary debridement at base hospital on twelfth day following initial debridement. Immediate split thickness skin graft. First dressing shown five days later (17 days after wounding). No chemotherapy for reparative surgery.

Revision of craniocerebral wounds when there is evidence of residual devitalized tissue or impending infection is followed by closure when feasible even if established infection is disclosed. Observations are being made relative to the earlier repair of peripheral nerve injuries. This is a procedure that may better be considered as early reparative surgery rather than late reconstructive surgery. The projected method of management includes revision and appraisal of the nerve injury at the time of secondary wound closure and in suitable cases repair as soon as satisfactory healing is established (two and one-half to three weeks).

To realize fully the potentialities of reparative surgery requires the introduction of a new concept in the organization of military surgery. The time-lag between wounding and initial surgery referred to as "the golden period"

has been greatly reduced by the organization of medical service in the forward area to this end. The time-lag between initial surgery and reparative surgery has now assumed an equal degree of importance. Just as every hour added to the time-lag between injury and initial surgery increases the loss of life and limb, so does every day added to the time-lag between initial and reparative surgery. Four to ten days is the "golden period" to close wounds, reduce and fix fractures, remove retained missiles and carry out other procedures to prevent or abort infection. To fail to take cognizance of the potentialities of early reparative surgery at the base in the future plans and operations will be as unthinkable as a failure to plan for the removal of the wounded from the field of battle.

Air evacuation between Army and Base, early establishment of general hospitals in close support of an advancing Army, sorting of casualties on arrival at Base so they may have the benefit of expert and specialized surgical management, are matters of administrative import. Education of surgeons to undertake new and unfamiliar procedures, the correction of anemia by whole blood transfusion so that essential surgery may be undertaken at an early date and increased attention to rehabilitation procedures are some of the major problems faced by professional personnel.

Particularly important is the concept that the surgical management of a wounded soldier from the field of battle to his ultimate hospital disposition within the theater demands continuity of policy and effort. A wounded man is not like a box of ammunition or a crate of rations that can be deposited at the boundary of an echelon and responsibility dismissed. Only by co-ordination of policy and methods between echelons can military surgery attain its full stature.

It is a satisfaction to note the contrast between the present concept of wound management and the doctrines in vogue scarcely a year ago. The closed-plaster management of wounds and fractures was designed to conserve life but exacted a high price in skeletal and soft-part deformity. Its use is now limited to certain cases with established infection of bone or with massive defects of soft parts compounding a fracture site. Recommendations that minimized the necessity for a complete initial wound operation or sought to delay it (wound trimming, "salting down with sulfa drugs," *etc.*) accepted suppuration as inevitable in a considerable proportion of cases and relied on chemotherapy to hold sepsis within bounds. Resuscitation measures that relied on plasma alone to compensate for loss of whole blood prolonged life but tied the hands of the surgeon in the performance of life-saving surgery. These and other earlier concepts were but faltering steps toward what will emerge as the ultimate scope of surgery as developed in the present war.

# VASCULAR INJURIES OF WARFARE\*

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WHITE SULPHUR SPRINGS, WEST VIRGINIA

ACCOUNTS OF INJURY to blood vessels in warfare have been recorded since the beginning of history, and the attention of surgeons has of necessity been primarily directed towards their treatment because of their often fatal nature. The arrest of hemorrhage and the preservation of an adequate arterial supply to the extremities have been, in fact, the main concern of military surgeons since the dawn of recorded medical history, and numerous papers concerning vascular injuries have appeared in medical literature following every war. The number of such injuries has increased steadily, probably due to the introduction of higher velocity projectiles of smaller caliber. In addition to the ordinary wounds caused by machine gun, rifle bullets and shrapnel, a great many multiple injuries are being produced by the fragmentation of land mines, grenades and aerial bombs. These latter may produce as many as one hundred small individual wounds scattered over the body without causing death, thus increasing the chance of trauma to blood vessels. It is, therefore, to be expected that the sequelae of these injuries will be encountered more numerously than ever before. Moreover, improved methods in the control of hemorrhage, shock, and infection have preserved more individuals for subsequent observation and study.

In order to bring about more highly specialized treatment of certain surgical conditions, the Surgeon-General has established centers for their treatment. In view of the fact that Ashford General Hospital is designated as one of two centers for vascular surgery, no doubt a larger proportion of this type of injury is seen at this institution.

For descriptive purposes, vascular injuries as result of war wounds may be divided as follows:

- 1 Those in which the blood vessel is completely severed or in which vasospasm exists to such an extent as to so impoverish the blood supply that death of the part or useless fibrosis results.

- 2 Activation of previously existing blood vessel disorders or tumors, such as congenital nevi and preexisting vascular injuries.

- 3 Partial severance of a vessel producing a false aneurysm or arterio-venous fistula.

Numerous instances of all these lesions in varying degree have been observed, and illustrative types of each are described here in detail.

## I—ARTERIAL OCCLUSION

Arterial occlusion, either complete or partial, may result from several

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factors, all traumatic in nature. A vessel may be completely severed requiring ligation, and unless collateral flow is adequate, gangrene or a condition not unlike Volkmann's ischemic paralysis will result. Similarly, the vessels may be occluded by compression of a hematoma or some infringement upon its lumen by fractured bones, or by too tight splinting or prolonged and improper application of a tourniquet. While the factor of venous occlusion in producing this state cannot be overlooked, surely the clinical manifestations, generally described as Volkmann's paralysis, do occur following arterial occlusion, as will be shown in illustrative cases.

A vessel may, likewise, be completely or partially occluded by spasm. A number of factors may bring about a reflex vasospasm and produce the picture classically described by Leriche. This may occur where only the outer wall of an artery has been injured or even in cases of trauma to adjacent tissues without actual injury to the vessel itself. While vasospasm is a natural protective response to trauma, it may be so extensive in character that death of a part or its crippling may result. It may be segmental, involving only a small portion of a vessel, or it may reflexly involve other vessels of an extremity or even produce a vasomotor imbalance of more than one extremity or even the whole body. Where the whole arterial tree of an extremity undergoes such a change interference with collateral circulation is pronounced, and under such circumstances the limb is white, numb, cold, pulseless and paralyzed. If relaxation occurs within a few hours, either spontaneously or through operative measures, the limb may return to normal, but if constriction persists, thrombosis will occur and varying degrees of trophic changes will result—gangrene or fibrosis with atrophy, stiffness of the joints, and a fixation deformity. An excellent account of these matters has been published by Griffiths<sup>1</sup> (1940), and, more recently, by DeBakey<sup>2</sup> (1944).

*Case 1—Ischemic contracture with gangrene of right hand following severance of axillary artery, median and ulnar nerves. Thrombosis of distal brachial vessels. Suture of median and ulnar nerves. No improvement in nutrition of hand following physiotherapy.*

This soldier was struck by a machine gun bullet in the upper inner aspect of the right arm May 6, 1943. The entire arm immediately felt numb, and he was unable to use it. He lost considerable blood. He was operated upon shortly afterwards, and it was found that the right brachial artery had been severed, but it was believed that the nerves were intact. Debridement of the wound was carried out. On the second day after the operation there was considerable swelling of the entire arm from the area of the wound to the finger tips. He developed blisters in the palm of his hand, and the tip of the right ring finger sloughed off. There was superficial sloughing in the palm. He entered Ashford General Hospital October 1, 1943. At that time the gangrenous areas were practically healed, but there was sensory and motor evidence of ulnar and median nerve paralysis. The arm, forearm, and hand were atrophic, and the latter was held in a fixed flexion contracture. On October 21, 1943 exploration of the lower axilla was done (Major Barnes Woodhall). It was found that the ulnar and median nerves were completely severed, and that the axillary artery had been divided and ligated. The divided nerves were sutured. The distal end of the divided

On September 6, 1943, two aneurysms, one of the lower brachial and the other of the ulnar artery, were excised on the left side (Captain Kremer, 26th General Hospital). One week later he began having intermittent attacks of arterial spasm in the left hand characterized by pain, cyanosis, and occasional blanching, particularly if he was exposed to cold. A week after this he noticed that the right hand became cyanotic, and this was soon followed by cyanosis of both feet, the color changes in all four extremities

'Y'

TEST SPINAL ANAESTHESIADATE 24 February 1944OSCILLOMETRYCONTROL

	Right	Left
Popliteal	75 at 100 mm	80 at 100 mm
Tibials	40 " 100 "	375 " 100 "
Foot	05 " 90 "	05 " 90 "

20 Minutes after Spinal

	Right	Left
Popliteal	70 at 110 mm	675 at 100 mm
Tibials	60 " 80 "	60 " 80 "
Foot	25 " 60 "	25 " 60 "

SKIN TEMPERATURES  
IN DEGREES FAHRENHEITROOM TEMP 76 °FCONTROL

	R	L
1st Toe	87.5	84.5
2d "	87.0	84.0
3d "	88.5	87.0
4th "	86.0	82.0
5th "	84.0	81.0
Plantar	84.5	83.0
Dorsum	90.0	88.0
Ankle	86.5	88.0
Midleg	91.0	91.0
Knee	87.0	88.0
Thigh	90.5	90.5

20 Minutes after Spinal

	R	L
1st Toe	92.5	94.0
2d "	93.0	93.0
3d "	93.0	93.0
4th "	92.0	93.5
5th "	92.0	94.0
Plantar	93.0	93.5
Dorsum	94.0	94.0
Ankle	93.5	94.0
Midleg	93.0	93.5
Knee	93.5	95.0
Thigh	92.5	92.5

FIG 4—Case 4 Showing increase in oscillations and temperature of the feet following spinal anesthesia

increasing but at times returning to normal. On September 27, 1943, a novocaine cervical sympathetic block was performed. This produced a warm dry hand lasting for three hours. A second block on October 13, 1943, produced a Horner's syndrome, with little change in his hand or arm. He was admitted to Ashford General Hospital December 3, 1943. *There was nothing in his history to indicate any vasomotor disturbances prior to being wounded on July 14, 1943, in spite of active duty in a cold climate.*

On examination, both hands to the wrists were markedly ruborous and cold. Perspiration was increased. Both feet assumed an ever-changing pattern of color beginning on dependency, with mottled areas of deep cyanosis alternating with blotches of deep rubor. The cyanosis was seen at the terminal digits over the phalangeal joints on the plantar surface of the toes and on the medial plantar side of the feet. The remainder of the feet was deep red in color. On complete dependency the plantar portion of the

feet and toes became so completely cyanosed as to resemble the dusky grayness of impending gangrene. There were no trophic changes.

The brachial blood pressure was 130/100. All pulses were present but were weak in both feet. On elevation of the feet palor of the toes was marked on the medial plantar surfaces. His face was intensely red especially over the malar prominences. The nose had areas of mottled cyanosis and redness, and the ears were intensely red in spite of being cool to palpation. Upon light scratching of both the chest and the intrascapular regions, a typical dermatographia was elicited with wheals and erythema. Oscillometric determinations and temperature readings before and after spinal anesthesia are shown on Figure 4. It will be noted that after elimination of constriction impulses the oscillations in the tibial regions almost doubled, and the readings in the feet increased five times. The readings under spinal anesthesia were practically twice that found in the normal individual. The skin temperatures rose from five to ten degrees in the toes and feet, about three to five degrees in the legs. The readings were above those seen in the normal individual.

**DISCUSSION**—The treatment of vascular occlusion, either from severance of a vessel or traumatic vasospasm, presents a problem of unusual difficulty. The final result and the ultimate prognosis will depend in the main upon the original treatment received shortly after the injury. In the first place, a tourniquet should never be applied if bleeding can be controlled otherwise, and if applied it should be as near the wound as possible. An Esmarch bandage is preferable to a rubber tube.

Every effort should be made to preserve the continuity of an artery, and in lateral lacerations repair may be possible. If ligation should be necessary, it should *not* be done in continuity but should be sectioned completely, since the division prevents peripheral arteriospasm and secures the best collateral circulation. Section and ligation of companion veins should likewise be carried out. Repair should be attempted only when it appears to be the sole means of saving a limb. Vasodilatation by means of sympathetic procaine block frequently repeated, or by sympathectomy, should be performed if the integrity of the circulation appears in doubt.

Other procedures, such as the use of plasma or blood to obtain an adequate blood pressure, the use of heparin to prevent thrombosis, and the position of the limb for maximum circulatory balance, should be employed if conditions do not otherwise contraindicate their use. In large lacerated wounds and in those accompanied by damage to other tissues such as bones and nerves, splinting is essential, but immobilization should be discontinued at the earliest possible moment and early motion instituted in order to prevent joint fixation.

In cases of traumatic vasospasm, therapy is directed to the removal of reflex vasoconstrictor impulses. This may be brought about by removal of traumatized tissue, periarterial sympathectomy or better still by procaine sympathetic block or sympathectomy.

In the late stages where contracture deformity has taken place, as illustrated by Cases 1 and 2, any progress toward recovery will be slow and the eventual outlook poor. Physiotherapy in the form of heat, massage, and whirlpool baths is indicated as are splinting and occasional plastic procedure to correct deformity.



Where vasomotor imbalance follows arterial injury, as in Case 4, the interruption of vasoconstrictor fibers by sympathectomy to one or more extremities may restore a proper balance and in any event should be tried provided there is temporary improvement following procaine block

## II—PREEXISTING VASCULAR LESIONS

It is the belief of many who have studied the subject that cirroid aneurysms, pulsating angiomas, and arteriovenous aneurysms are essentially the same condition, all being a form of abnormal communication between arteries and veins in varying degree. It is well known that vascular nevi, congenital telangiectases, or angiomas, in which the intermediary incidence of trauma has occurred, may be the starting point of disfiguring and disabling vascular tumors. Moreover, vascular injuries, apparently dormant or inactive, may, likewise, become activated by further trauma. It is to be expected, therefore, that war injuries, either as result of direct trauma or following long continued irritation, will give rise to such conditions in increasing numbers. That twelve instances of this nature have been seen at Ashford General Hospital in the past year bear out this assumption. Four of them are cited below in detail as examples. The seriousness of this lesion as a potential hazard must not be overlooked, for an apparently innocent lesion may be the source of a disabling defect requiring major surgical procedures, including amputation. Although trauma plays the major rôle in their inception, there are probably other factors as yet unexplained which have a part in their development. When contributing arteries and outgoing veins succeed in forming diffuse anastomosis through a cavernous bed, the lesion becomes nothing more than a diffuse arteriovenous fistula. While the existence of a congenital lesion can usually be elicited from the history, this abnormality need not always be present. A wound, particularly if inflicted upon superficial vessels, such as those of the scalp, face, fingers or toes, will often give rise to these diffuse tumors, and additional trauma such as bruising or prolonged irritation may contribute further to their development. In any outspoken example of this condition the clinical picture is such a striking one that the case is likely to be reported, and there is an extensive literature on the subject (Elkin,<sup>3</sup> Reid,<sup>4</sup> and Pemberton<sup>5</sup> )

*Case 5—A small, bluish, pigmented mass in right axilla, present since childhood. Ten months trauma from rifle recoil, with marked increase in size. Complete excision and skin graft*

This soldier is known to have a small bluish discoloration in his right axilla since childhood which had given him no trouble and which had increased only slightly in size. During ten months Army service the mass was subjected to the trauma caused by recoil of a rifle, and during that time the mass had markedly increased in size until it extended throughout the whole right axilla. Large dilated veins, easily compressible, covered an area about six inches in diameter (Fig 5). There was no bruit and no thrill. Numerous small venules were present in the skin of this region. On December 17, 1943 skin incisions were outlined which extended beyond the dilated blood vessels. The skin of this area was completely excised as were the subcutaneous tissues, down to and including the pectoral and axillary fascia. Numerous dilated veins communicated



FIG 5—Case 5 Appearance of hemangioma of axilla

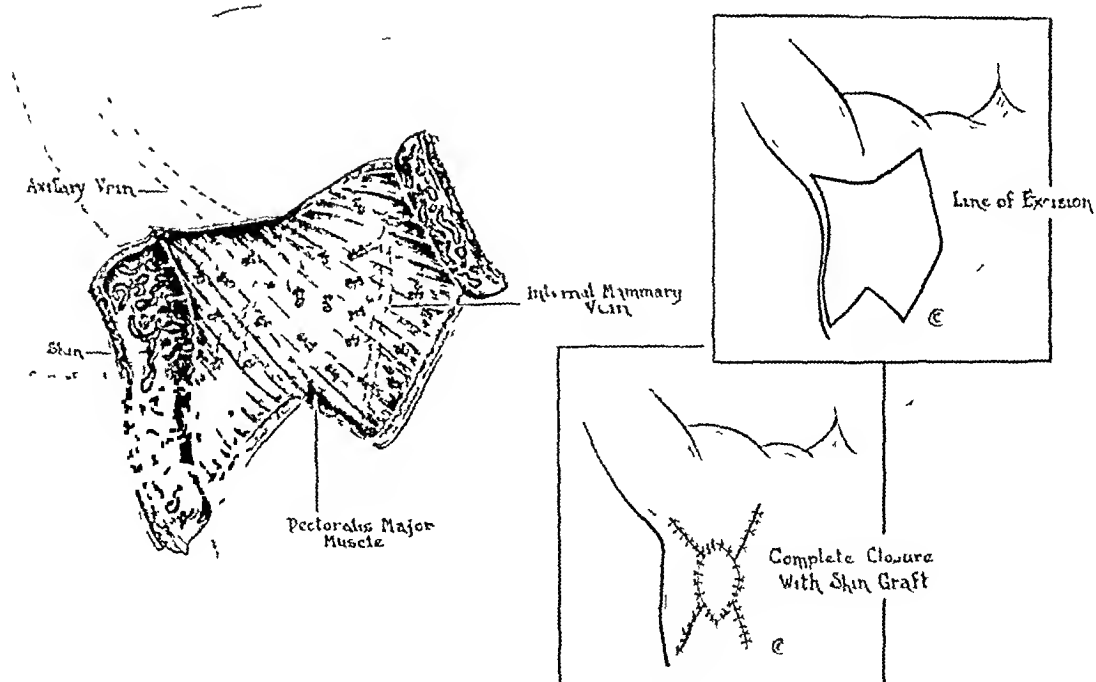


FIG 6—Case 5 Hemangioma of axilla showing line of excision and method of closure

with this area and entered, for the most part, the cephalic and axillary veins. After excision the skin could be partially closed and the remainder was covered with a skin graft (Fig 6). There has been complete recovery with no evidence of recurrence.

**Case 6—Childhood injury, sole of left foot, by glass. Diffuse arteriovenous fistula, sole of left foot involving plantar vessels noticed 30 years after original injury following excessive marching. Complete excision of fistula after preliminary ligation of posterior tibial and dorsalis pedis vessels.**

This 37-year-old Dental Officer stepped on a piece of glass in 1914, causing a one-inch laceration in the midplantar region of the left foot. Bleeding was profuse, but healing was uneventful. In 1938 he noticed the appearance of large blood vessels over the left foot and leg. He entered the Army in December 1943 with a "waiver for varicose veins." After three weeks of basic training, at which time he underwent



FIG 7—Case 6. A. Diffuse arteriovenous aneurysm, sole of foot, showing marked enlargement of veins.  
B. Showing appearance of the foot, one month after excision of the aneurysm.

# VASCULAR INJURIES OF WARFARE

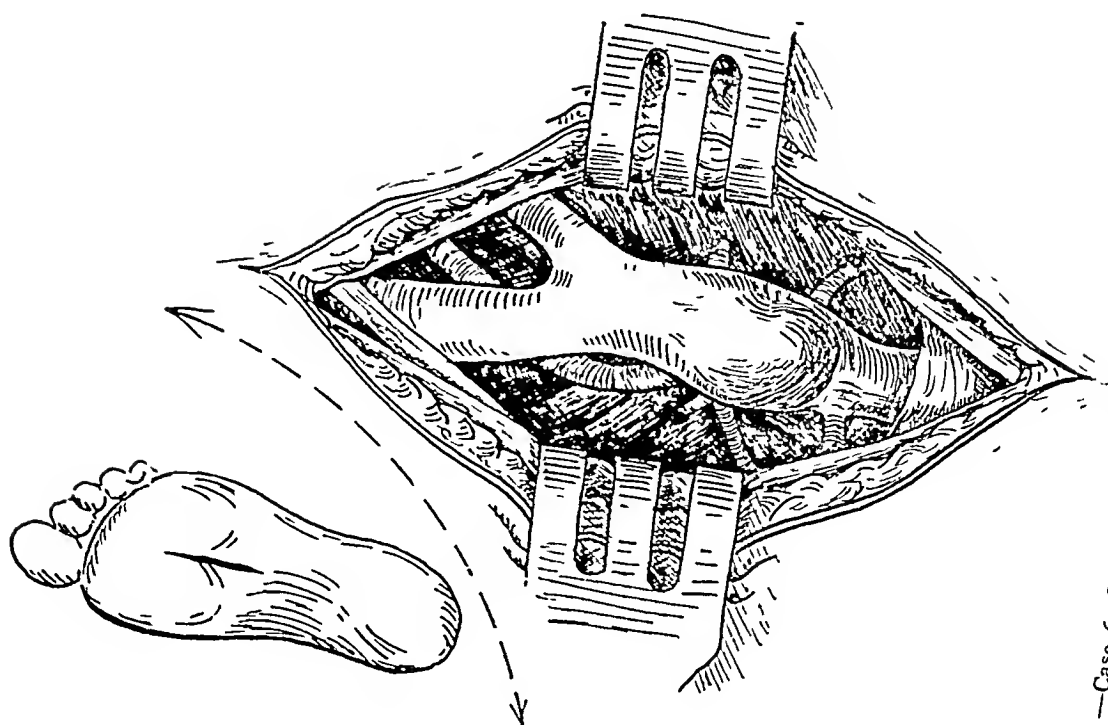
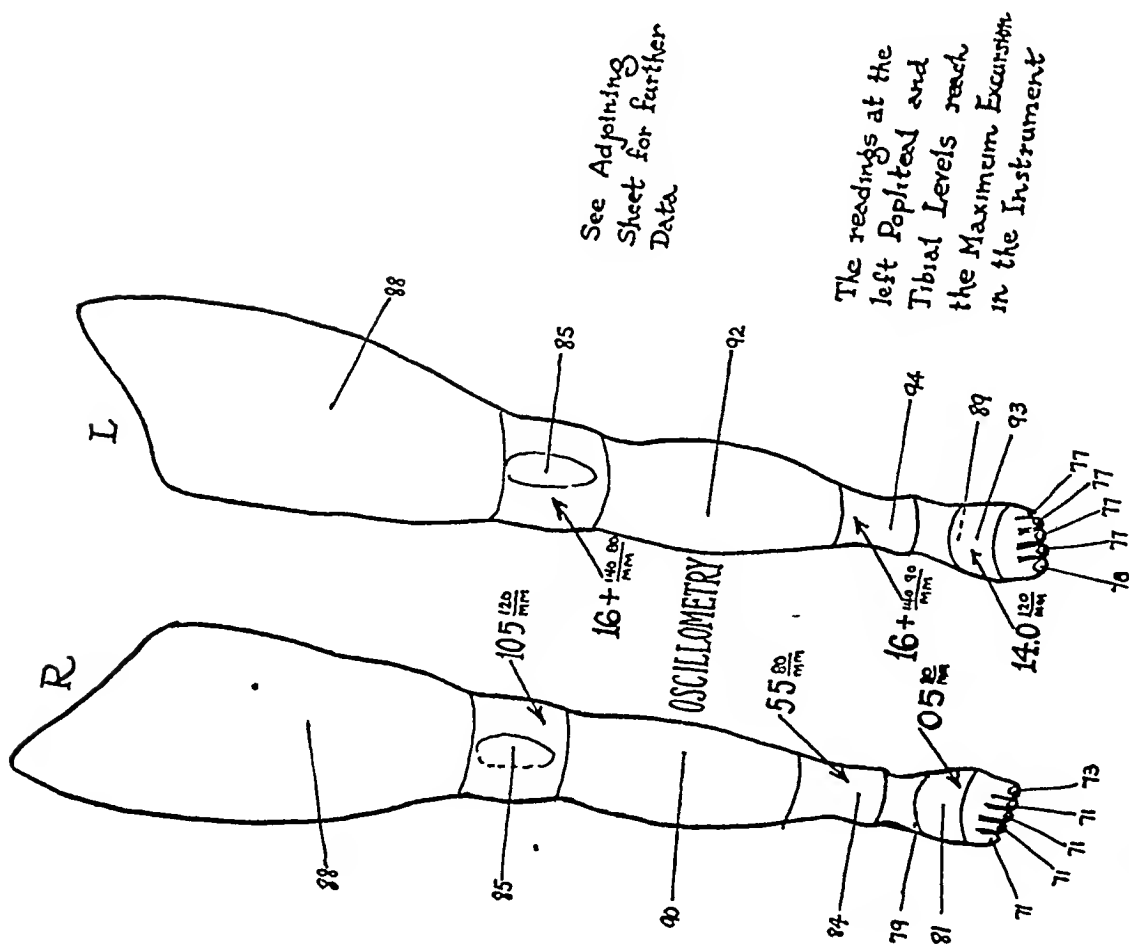


Fig 9—Case 6 Showing appearance of the aneurysm in the sole of the foot



## SKIN TEMPERATURES

Fig 8—Case 6 Showing increased oscillations and temperature of left leg and foot in case of diffuse arteriovenous aneurysm of sole of foot

considerable marching, he noticed pain and swelling in the bottom of his foot near the toes, and on examination he was found to have a bruit and thrill in this region and was referred to this hospital. On examination there was marked engorgement of the saphenous veins over the foot and leg (Fig 7 A). The left foot was warmer than the right. A continuous bruit, accentuated in systole, was most marked on the bottom of the foot but was transmitted to the whole leg. The posterior tibial and dorsalis pedis vessels were full and bounding. Increased temperature and oscillations of the left leg and foot are shown in the accompanying chart (Fig 8).

It is believed that this diffuse arteriovenous fistula had its origin in the previous injury which was thought at that time to be of trivial nature. The added trauma of marching brought about a rapid increase in its development.

Operation was performed February 15, 1944. Preliminary ligation of the posterior tibial and dorsalis pedis arteries was done. The former vessel was markedly increased in size and was tortuous. A longitudinal incision was then made for three inches on the sole of the foot just medial to the old scar. Numerous small vessels were encountered. The plantar fascia was opened, and the short flexors of the foot were separated. The flexor hallucis longus was retracted medially, and the deep plantar space exposed. Several large arteries and veins, which were pulsating, together with numerous tributaries, were found in this area. Distal to this, large arteries and veins were disclosed. All of these were dissected free from surrounding tissues, ligated, and divided, and the fistula removed *in toto* (Fig 9).

The patient's recovery from operation was uneventful. The large dilated veins previously noted disappeared in a period of about three weeks (Fig 7 B). There has been no return of bruit and thrill, and he returned to duty May 1, 1944.

*Case 7—Crushing injury to the left foot in 1937. No fracture. Recovery in eight months. Diffuse arteriovenous fistula, sole of left foot involving plantar vessels, noticed 1941 following marching. Complete excision of fistula after preliminary ligation of posterior tibial and three dorsal vessels.*

This 23-year-old soldier sustained a crushing injury to the left foot in civilian life in 1937. No fractures were found, and the foot was strapped. There was considerable swelling and pain for about eight months. In November, 1941, after one year in the Army, he first noticed a "humming" in his foot, with pain and swelling. He had been subjected to the strenuous activities of a soldier on Guadalcanal, and the symptoms all increased and became aggravated by marching. He entered Ashford General Hospital February 29, 1944. Examination was normal except for the left foot and leg. The left foot was slightly swollen. The superficial veins were dilated and tortuous, and a thrill could be felt over the dorsal and plantar regions, most marked on the plantar surface (Fig 10 A). There was a loud continuous bruit with systolic accentuation over the entire foot which was transmitted up the leg to the midcalf posteriorly. The thrill and murmur could be obliterated by pressure over the posterior tibial artery. There were several pulsating vessels on the dorsum of the foot. The left foot showed increased warmth and increased oscillations (Fig 11).

Operation was performed March 4, 1944. The posterior tibial vessels were exposed behind the medial malleolus and ligated and cut. The dorsalis pedis artery was treated in a similar manner. A longitudinal incision was made in the sole of the foot about four inches long over the region of the fourth metatarsal bone. The plantar fascia was divided longitudinally, and the small muscles of the foot were separated until the plantar vessels were reached. Large posterior tibial arteries were found entering this region and communicated with a dilated venous sac. Distal vessels, both arteries and veins, as well as lateral communications were also encountered. All of these were pulsating in spite of the previous ligations. Since they appeared to communicate with abnormal dorsal vessels, two additional incisions were made on the dorsum of the foot, and vessels in this region were ligated there. The sac, with its communicating arteries and veins, was then excised and removed after ligating and cutting all communicating branches (Fig 12).

DATE 2 March 1944

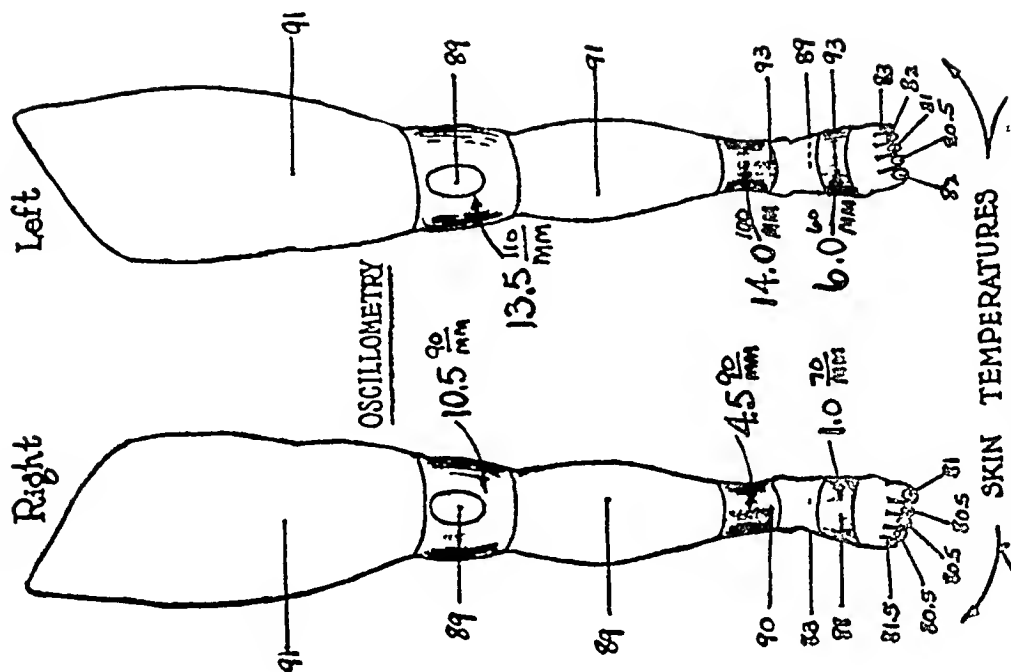


FIG 11—Case 7 Showing increased oscillations and temperature on the left



FIG 10—Case 7 A Showing engorgement of veins of foot  
B Showing appearance of foot after excision of the aneurysm

All wounds were closed with silk. At the end of operation there was no evidence of a bruit or thrill, and the toes were warm and pink. There has been no return of the bruit and thrill, and the dilated veins about the foot have disappeared (Fig 10 B)

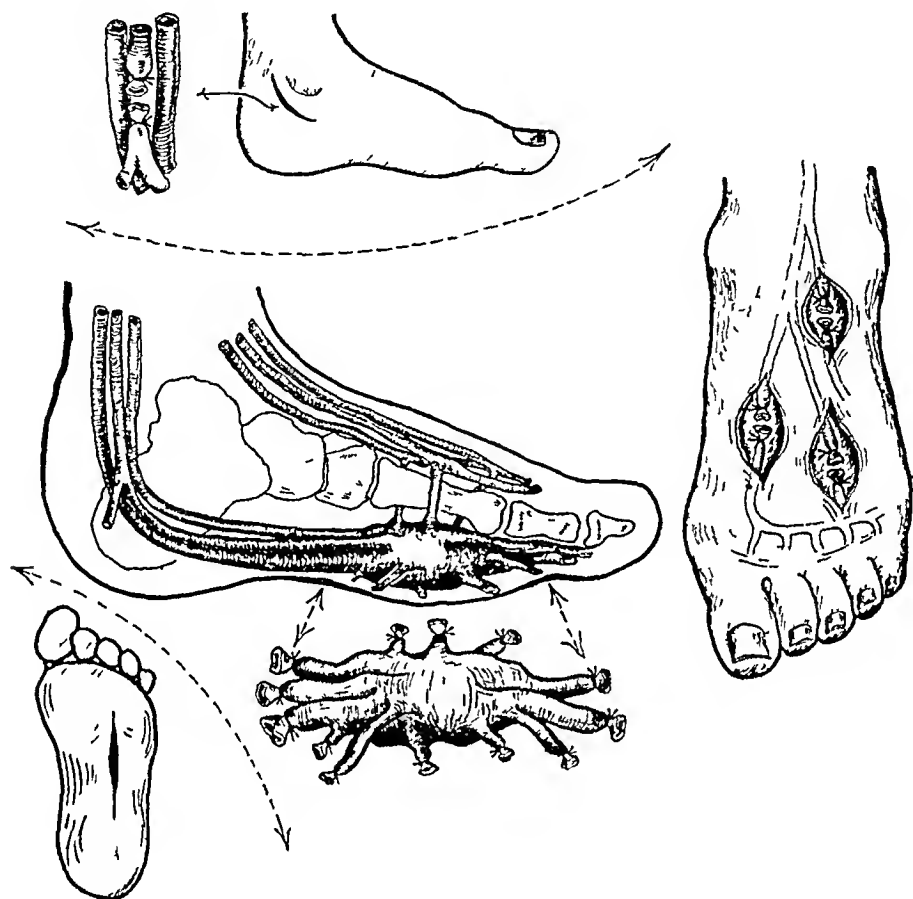


FIG 12—Case 7 Showing, schematically, the preliminary ligation of vessels and complete excision of the lesion

**Case 8—Small hemangioma, sole of right foot since childhood** In July, 1943, the foot injured by jumping into a fox hole, followed by gradual increase in size of tumor. Unsuccessful attempt to excise tumor. Severe hemorrhage necessitating amputation.

In infancy it was noted that patient had a mass on the plantar surface of the right foot. It caused no discomfort and did not limit his activity. At age 12, it was noticed that the right leg was slightly longer than the left. Six years before entrance into this hospital he noticed prominence of the veins of the left foot and ankle. On July 25, 1943, in action in Sicily, he struck the plantar surface of his foot when he jumped into a fox hole. Following this there was pain and gradual increase of the swelling on the plantar surface of the foot. On August 10, 1943, an unsuccessful attempt was made to remove the tumor, and the posterior tibial artery was ligated.

On examination at Ashford General Hospital there was an expansile, pulsating, compressible mass involving the whole sole of the right foot, extending from the heel to the toes (Fig 13 A). There was a continuous thrill and bruit over this area accentuated in systole. The veins of the right leg were dilated. The right foot was warmer than the left, and the right leg was 6 cm longer than the left. There were marked increased oscillations on the right side.

## VASCULAR INJURIES OF WARFARE

On December 20, 1943, an attempt was made to excise the aneurysm after ligation of the posterior tibial and dorsalis pedis vessels. The whole plantar surface was a mass of dilated venous and arterial sinuses. Hemorrhage from them could only be controlled with a tourniquet and, after a three-hour attempt to ligate them individually and *en masse*, it was felt that any procedure other than amputation might prove fatal. Amputation was accordingly performed.

Injection of the arterial tree of the amputated foot is shown in Figure 13 B. Even after ligation of a large number of vessels, numerous dilated sinuses are still present.



FIG 13—Case 8. A. Appearance of the foot before final operation. The posterior tibial artery has been ligated and unsuccessful attempt made to extirpate the lesion.  
B. Arteries of the amputated limb injected with mercury. Note numerous collaterals about the points of ligation and the increased vascularity of the whole foot.

DISCUSSION—A variety of operative procedures has been employed in the treatment of these conditions—ligation of the main blood supply, multiple circumferential sutures, obliteration of the lesion with the cautery, or injection of thrombosing or scar-forming sclerotics. The only universally suc-



cessful method is complete extirpation, since recurrence notoriously follows halfway measures. Moreover, operation should be carried out in the early stages of the development of the lesion. Otherwise the rapidity of its growth and the extent of involvement may place its removal outside the domain of surgery or else require sacrifice of a part, as illustrated in Case 8. Under any circumstances, the operator is confronted with a problem requiring not only meticulous skill and care in its performance, but one demanding the courage to attempt an ordeal which may be fatal because of hemorrhage, or which may require amputation.

### III—ANEURYSMS

It is not the purpose of this paper to discuss in detail the diagnosis and treatment of aneurysms or arteriovenous fistulae. Openings in blood vessels produced by small missiles may for a time present no symptoms and no physical signs other than a bruit. For that reason these lesions are frequently overlooked, particularly if more striking or extensive injuries are present. The value of auscultation as a means of determining the presence of these lesions cannot be too strongly stressed. In the inception of any vascular injury, external or internal bleeding may be severe, and the immediate care quite correctly is directed to the control of hemorrhage. On the other hand, bleeding may be slight, even though a major vessel is involved, and in the absence of severe laceration it may be controlled by pressure of the soft tissues and thus a pulsating hematoma or false aneurysm be formed. In the presence of a large number of casualties and under battle conditions, such as front line hospitals are now working, a diagnosis, though incomplete, or even incorrect, may be carried by a wounded soldier for some time. This does not imply that proper treatment has not been given, but it does entail upon those who are working in the Zone of Interior or in general hospitals distant from the battle field the necessity of careful examination uninfluenced by any previous diagnosis. Moreover, it is a well known fact that a vascular lesion may develop slowly to the point of recognition. For example, an arteriovenous fistula present from the onset of an injury may not show characteristic signs until edema and tissue hemorrhage have been absorbed. It is well to remember that blood vessels are usually accompanied by nerves, and that nerve lesions, which are so striking in their immediate manifestations, may mask or cause to be overlooked accompanying blood vessel trauma. Inconspicuous wounds may, likewise, involve blood vessels and are frequently overlooked through failure of the examining surgeon to suspect their presence, or because his attention has been directed elsewhere to a seemingly more important lesion. Aneurysms of various types will be overlooked unless *every* wound is carefully examined, particularly by auscultation.

The differentiation of a false arterial aneurysm and an arteriovenous fistula is of extreme importance since the sequelae, the general and local effects, as well as the treatment of the two conditions, differ greatly. The differential diagnosis is not always easy but as a rule an arteriovenous com-

munication is characterized by a *continuous* thrill and a *continuous* machine-like bruit accentuated in systole, whereas, in the false aneurysm there is a slight but distinct pause between the systolic and diastolic phases, or the bruit may be heard only in systole. In the case of a fistula the swelling is usually less pronounced although some fistulae communicating through a false sac may give rise to a tumor of considerable size.

The dilatation of veins about and distal to a fistula, the slowing of the pulse following its obliteration, and the trophic changes resulting from an impoverished blood supply distal to it are further differentiating points. In large fistulae or in those close to the heart, cardiac dilatation with subsequent failure is likely to follow. While time should be allowed for the development of collateral circulation, operation should not be delayed until cardiac failure has supervened. The enlargement of the heart and its rapid return to normal size following excision of this lesion are strikingly shown in Figures 14 and 16.

**Case 9**—*Femoral A-V fistula, resulting from rifle bullet on September 21, 1943. Cardiac enlargement with beginning failure. Excision of fistula. Rapid return of heart to normal size.*

This 21-year-old soldier was struck by a through-and-through rifle bullet in the right thigh September 21, 1943. There was very little bleeding. The wound was dressed shortly afterwards, and healing took place in about ten days. About one month afterwards he noticed fullness and swelling in this region, and about that time the presence of an aneurysm was noted.

He entered Ashford General Hospital February 5, 1944. There was some swelling of the right thigh, particularly on the inner medial aspect. In this region a distinct continuous thrill could be felt. He complained of fullness in the right thigh, swelling of the right lower extremity, pain in the right leg on walking, and dyspnea on exertion. The swelling of his thigh was most marked on the inner and middle aspects. The whole leg was swollen, and there was pitting edema of the right ankle. The veins of this leg were enlarged. A distinct thrill could be felt over the whole inner aspect of the thigh. A bruit, most marked in this region, was transmitted up to the groin and downward to the midleg. It was continuous but accentuated in systole. Obliteration of the femoral artery by pressure reduced the pulse rate from seventy-eight to forty-eight. Roentgenogram of the heart showed left ventricular enlargement (Fig 14).

On February 9, 1944, quadruple ligation and excision of the fistula were done. The proximal artery was greatly dilated as were all the veins in the region of the fistula. The distal artery was small. Numerous collateral vessels were found in the region of the fistula. All vessels in this region were tied and cut, and the fistula was completely excised (Fig 15). Postoperative course was uneventful. Roentgenogram of the heart made one week after the operation showed that the heart had returned to normal size (Fig 14).

**Case 10**—*A-V aneurysm, right posterior tibial vessels with communication through interosseous membrane. Ligation of all communicating vessels. Obliteration of fistula by multiple mattress sutures. Recovery.*

This soldier sustained a bullet wound of the right leg on March 31, 1943. The missile entered the posterolateral aspect of the leg five inches below the knee and made its exit on the inner lateral aspect. Bleeding was profuse but was controlled by a pressure bandage. On April 2, 1943, an incision was made on the anterior surface of the leg, and he was told that an artery was ligated. There was a partial paralysis of the peroneal nerve which had largely disappeared by October, 1943. In November, 1943,

the presence of an arteriovenous fistula was noted, presumably of the posterior tibial vessels, and he entered Ashford General Hospital December 1, 1943. Examination on admission was negative except for the right leg. The leg was swollen from the knee downward, and there was pitting edema of the ankle. An expansile pulsation was present in the area just below the popliteal space and in the line of an old incision on the anterior surface between the tibia and fibula six inches below the knee. In both areas there was a continuous thrill and a loud continuous bruit accentuated in systole. The bruit was transmitted over the whole leg, foot, and thigh. Obliteration of the

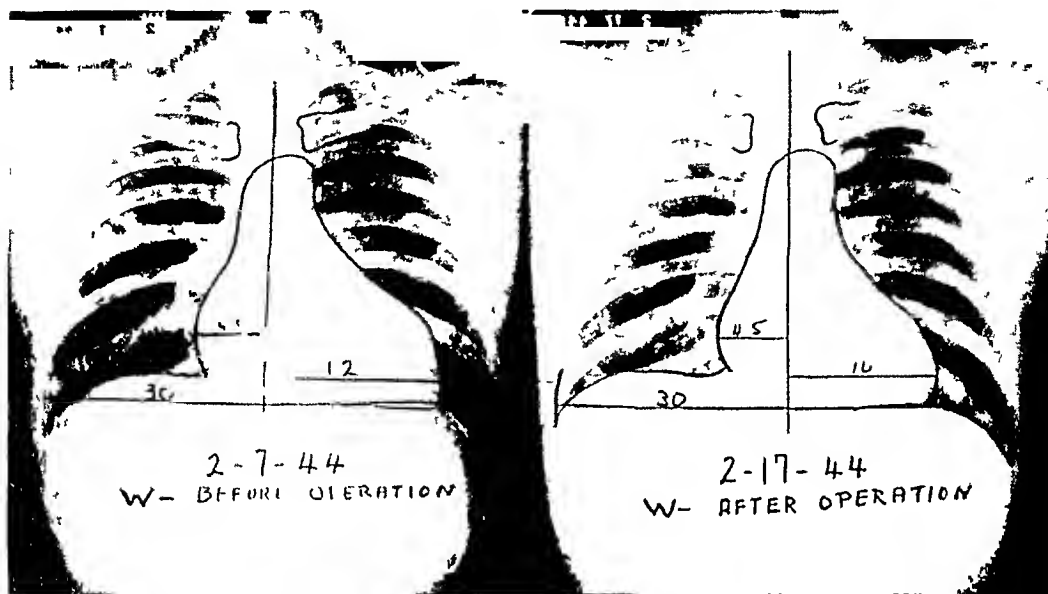


FIG 14—Case 9 Showing enlargement of the heart and rapid return to normal following excision of arteriovenous fistula

popliteal artery by pressure reduced the pulse from 94 to 80. Neurologic examination was negative except for slight weakness of the extensor hallucis longus, the tibialis anticus, and hypesthesia over the lateral aspect of the foot. Oscillations were markedly increased in the whole right lower extremity. Examination of the heart showed moderate left ventricular enlargement (Fig 16). Operation was performed December 15, 1943. Incision was made in the popliteal space and continued downward to the midcalf. The popliteal artery and vein were identified and temporarily occluded with a ligature. Both vessels were markedly enlarged. Another incision was made over the course of the anterior tibial vessels overlying the interosseous membrane at its upper end, and a large pulsating sac was uncovered in this region which apparently communicated through the membrane with the main sac on the posterior surface of the leg. The posterior incision was then dissected further, and a large sac into which numerous communicating arteries and veins entered was found. All of these vessels were separately ligated and cut, as were the proximal vessels previously identified. In an attempt to remove the sac in its entirety severe bleeding was encountered, evidently arising from other communications. This bleeding could not be controlled by individual ligation of vessels, and the whole sac was, therefore, obliterated and infolded by a number of heavy mattress sutures. This controlled the bleeding and obliterated the bruit and thrill. The wound was closed with silk. The patient's recovery was uneventful, and he returned to duty April 1, 1944. Enlargement of the heart previously noted returned to normal (Fig 16).

**Case 11—Left brachial aneurysm following gunshot wound. Paralysis of median, radial, and median cutaneous nerves from pressure. Complete division of ulnar nerve. Excision of aneurysm. Suture of ulnar nerve.**

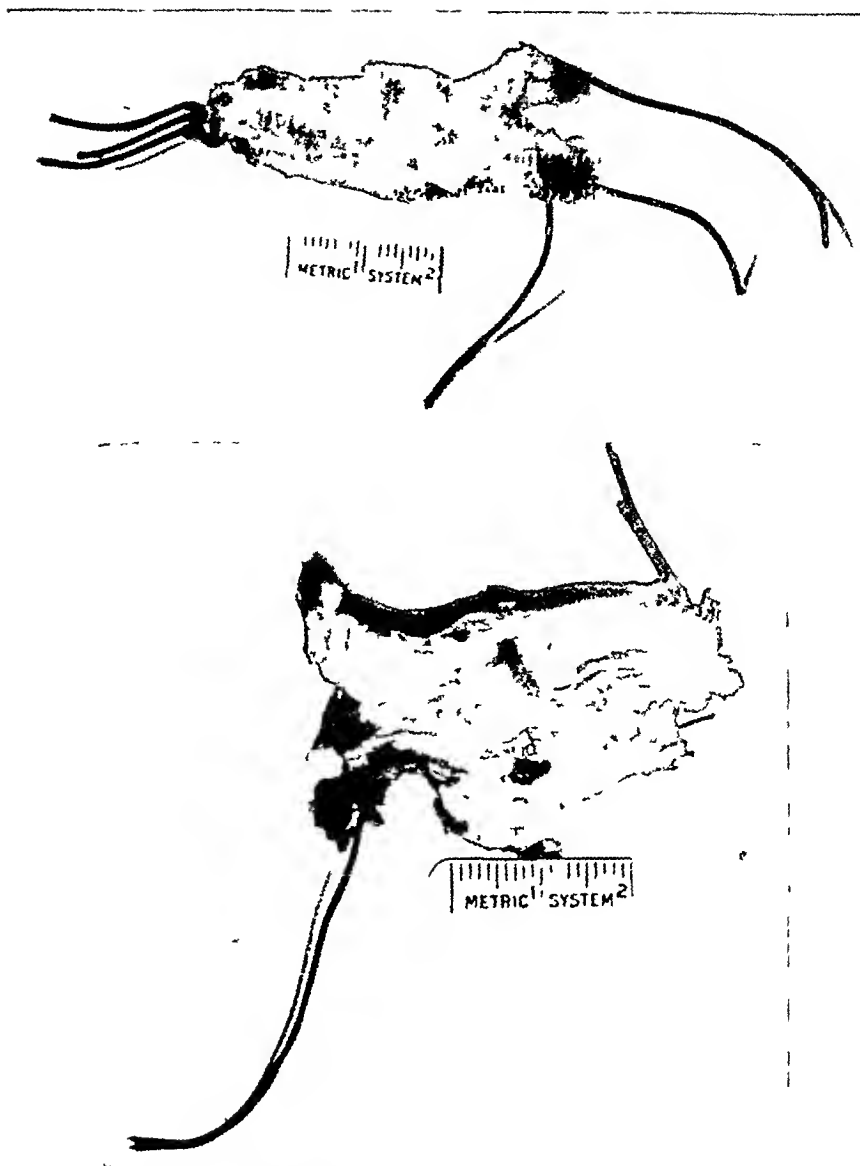


FIG 15—Case 9 A Arteriovenous fistula excised  
B The fistula opened showing the artery (above) communicating with the vein through a common sac

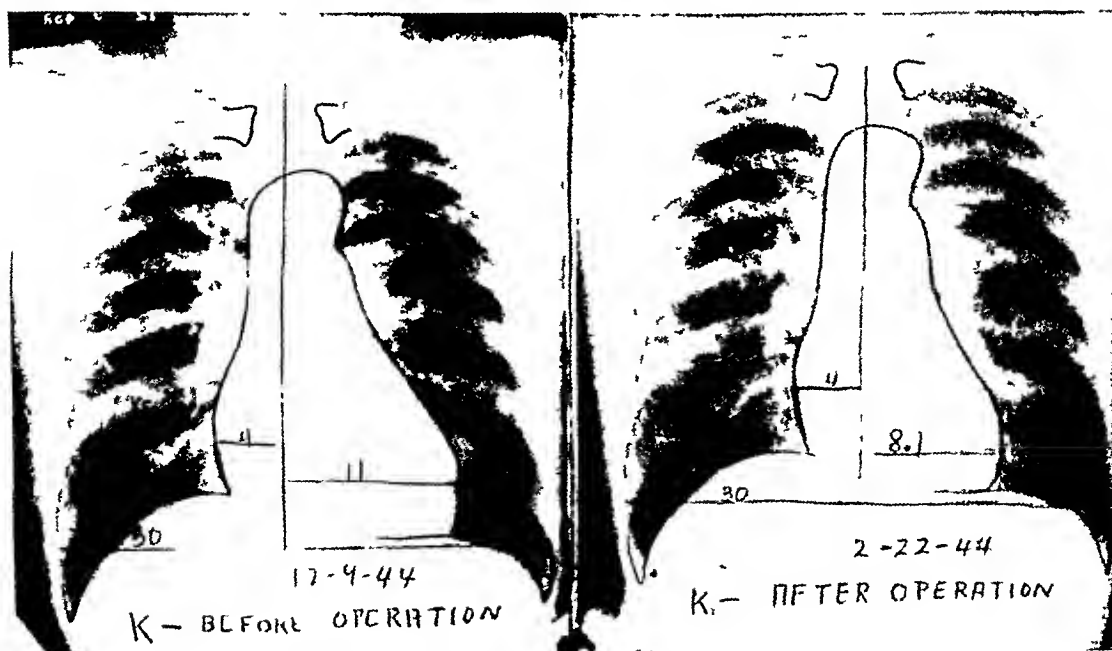


FIG 16—Case 10 Showing enlargement of the heart and return to normal size following excision of an arteriovenous aneurysm.

This patient was wounded, November 19, 1943, by fragments of artillery shell. He received wounds in the left shoulder, left arm, and left hand and face. There was considerable bleeding from the wound in the left arm which was situated just below the axilla. He immediately noticed numbness of the hand and inability to use it. He was evacuated from the line of fire, and his wound were debrided and an encasement applied. He was eventually evacuated through hospitals to Ashford General Hospital where he arrived March 9, 1944.

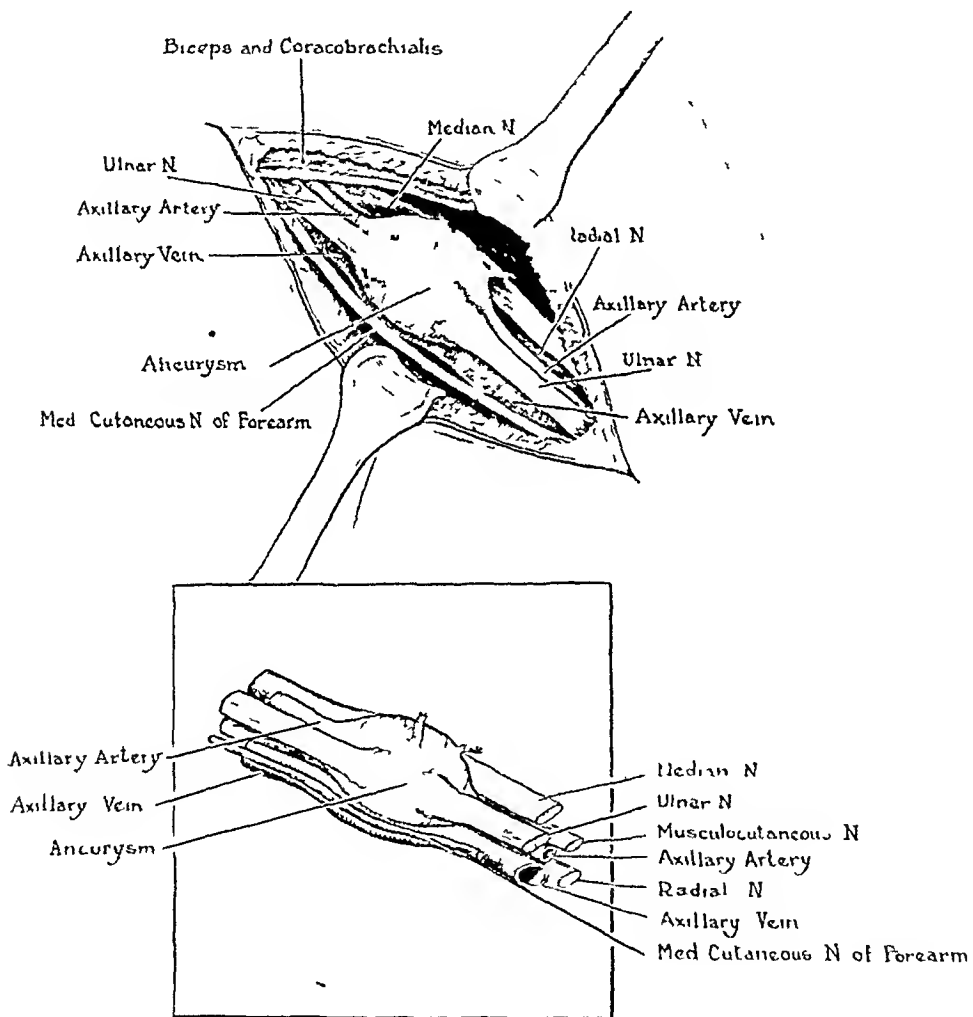


FIG 17—Case 11 Showing aneurysm of brachial artery with severance of the ulnar nerve and pressure paralysis of other nerves in this region

At the time of admission all the wounds were healed. Aside from the left upper extremity, examination was unimportant. In brief, examination showed complete paralysis of the median and ulnar nerves and a partial paralysis of the musculocutaneous and radial nerves. Along the medial aspect of the upper third of the left arm was a scarred wound measuring 8 cm in length. In the left axilla near the anterior axillary

fold was a pulsating mass 3 cm in diameter. There was no thrill, but a systolic bruit could be heard over it. The radial pulse was weak.

Operation was performed on March 17, 1944. An incision was made along the anterior border of the axilla, and the pectoralis major muscle was exposed and retracted upward. The vessels and nerves of the arm just below the axilla were exposed, and the proximal and distal brachial arteries connecting with the aneurysm were isolated and temporarily occluded with ligatures. The nerves in this region were firmly adherent to the aneurysm, stretched over it, and subjected to its pulsation. They were dissected



FIG 18—Case 12. Arterial aneurysm of axillary artery with paralysis of nerves from pressure

free from it with considerable difficulty. It was discovered that the ulnar nerve was completely severed at the medial side of the aneurysm and that the hiatus between the severed ends was filled with scar tissue (Fig 17). After isolation of the ulnar, median, radial, and median cutaneous nerves, the aneurysm was ligated proximally and distally and removed. The ends of the divided ulnar nerve were freshened and sutured with silk and tantalum. (Major George L. Maltby)

*Case 12—False aneurysm, axillary artery, following shrapnel wound. Pressure paralysis of medial, radial and ulnar nerves. Excision of aneurysm. Neurolysis. Sensory and motor improvement.*

On September 23, 1943, this officer was struck with multiple shrapnel fragments on the anterior chest wall, left elbow and left axilla. There was immediate loss of motor power of the hand and loss of sensation proximal to the elbow. There was very little bleeding, but there was considerable swelling in the axilla. There was some return of sensation in the hand and arm shortly after the injury. His wounds healed without difficulty.

He entered Ashford General Hospital December 1, 1943. Examination was essentially negative except for the left upper extremity. In the left axilla there was an oval



FIG 19—Case 12 Appearance of the axillary aneurysm after excision Note groove made by median nerve

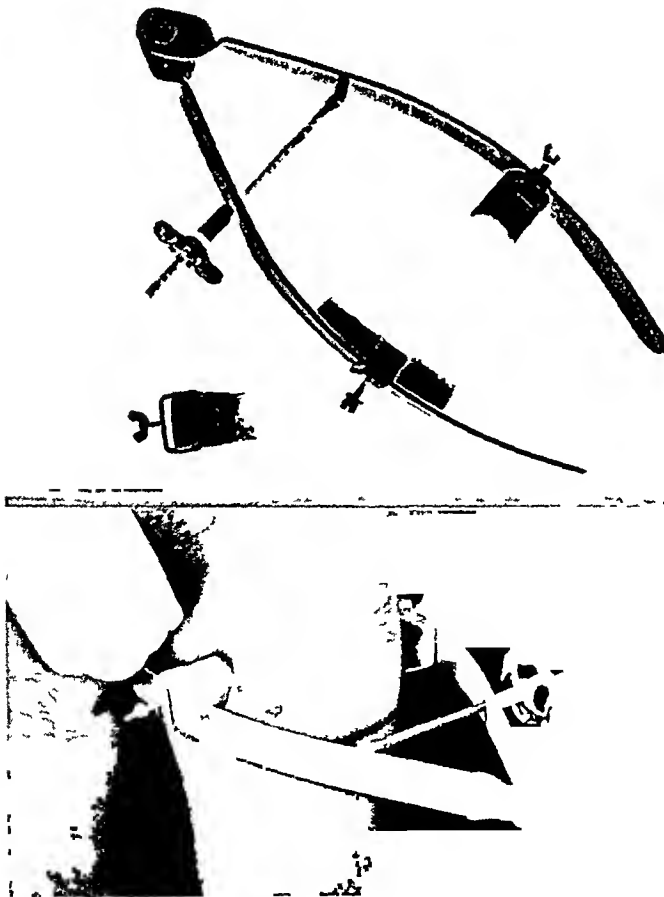


FIG 20—A The Matas compressor This is an inexpensive and easily constructed instrument  
B The compressor in place on the femoral artery

## VASCULAR INJURIES OF WARFARE

mass, 5 x 3 cm, which pulsed with systole (Fig 18) There was no thrill, but a harsh systolic bruit could be heard over it With pressure on the axillary artery above the mass the pulsation and bruit could be partially diminished Upon tapping the mass paresthesia developed over the entire hand The radial pulse was weak There was hypalgesia and scattered areas of anesthesia over the peripheral distribution of the ulnar, median, radial, and medial cutaneous nerves of the forearm Motor power of the muscles of the hand and arm was weak, and there was considerable stiffness of the joints It was apparent that the axillary artery had been injured and was the seat of aneurysm Neurologic examination indicated multiple nerve injuries, but of a type suggesting pressure rather than actual severance

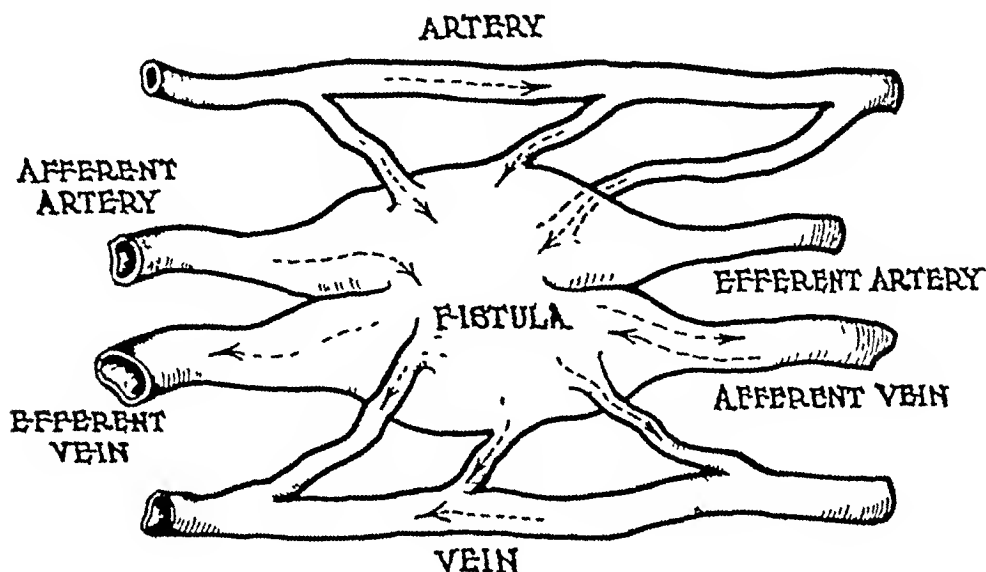


FIG 21—Schematic drawing to show communications of arteriovenous fistula and necessity of not only quadruple ligation but complete excision with all branches

Operation was performed December 14, 1943 An incision was made along the anterior border of the axilla and extended down the arm about three inches The axillary fascia was opened, and the axillary artery exposed above and below the aneurysm, and temporary ligatures were placed about the vessel The median nerve ran directly over the aneurysm and grooved it (Fig 19) Except for flattening and some fibrosis the nerve was normal The ulnar nerve was adherent to the aneurysm on its medial surface and the radial nerve posteriorly These nerves were freed from the aneurysm which was then ligated both proximally and distally and removed Patient returned to duty as a staff officer six weeks later, and he reports that there has been a gradual improvement in the motor and sensory function of the arm and hand

**DISCUSSION**—Certain basic principles must be observed in the treatment of these conditions Such a lesion is never a matter of emergency unless it is rapidly progressing in size, or has ruptured, or unless heart failure is impending Time should be allowed for the development of collateral circulation about an arteriovenous fistula, usually a matter of three or four months In an arterial aneurysm the use of artificial means to develop collaterals, usually proximal compression of vessels either manually or with the compressor devised by Matas, should be employed (Fig 20) Where nerve lesions accompany aneurysms, complete excision of the lesion, together with neurolysis and nerve suture, should be carried out in a single operative procedure Where *large* arterial aneurysms exist without accompanying



nerve damage the obliterative endo-aneurysmorrhaphy of Matas is the operation of choice. This type, however, is usually the result of arteriosclerosis or syphilis, and is, therefore, less often encountered in young soldiers.

The effect on the heart, the general circulation, and the part affected, demand that arteriovenous fistulae be completely eliminated. The manner of its obliteration is of importance because if the operation is incompletely performed recurrence is apt to take place. On theoretic grounds it would seem best to repair the opening in both artery and vein, but this is technically difficult and may result in secondary hemorrhage, thrombosis, or recurrence. Since collateral circulation is usually abundant, complete excision with ligation of all communicating vessels is the method of choice. Ligation without excision usually results in the recurrence since the fistula will be established rapidly through collaterals (Fig 21). If excision is impossible because of the anatomical location as in Case 10, or because of uncontrollable hemorrhage, recourse may be made to infolding the fistula with heavy mattress sutures. The operation should be carried out with the greatest care because of the number of vessels involved and because their thinness and friability may lead to uncontrollable hemorrhage. The operation is best performed without the use of a tourniquet since individual blood vessels can be better isolated and complete excision more thoroughly accomplished. Moreover, since the operation is frequently a prolonged one a tourniquet would have to be released during the course of the procedure. Continuous spinal anesthesia has been generally employed in operations upon the lower extremity, or intravenous sodium pentothal or ether in procedures in other locations.

#### SUMMARY

Illustrative cases are presented showing three main types of arterial injury, namely

- 1 Arterial occlusion from severance of vasospasm
  - 2 Blood vessel tumors and injuries activated by trauma
  - 3 Aneurysms and arteriovenous fistulae
- Diagnosis and treatment of these conditions are discussed

Illustrative drawings were made by Captain J W Kahn, M C, and Corporal Vincent Destro. Photography was done by Captain Floyd B Hall, M A C

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DISCUSSION—LT COL CLAUDE S BLCK, M C, Cleveland, Ohio I wish it were your privilege, as it has been mine on several occasions, to visit the Ashford General Hospital. There you would find a surgical service with surgical specialties that would compare very favorably with the surgical services of our best civilian hospitals. You would find there a group of vascular cases that, I daresay, cannot be equalled anywhere else in the world. In the operating room you would find surgical technique of the finest quality.

I might comment briefly on the incidence of arterial spasm. We are acquainted with vascular spasm developing without any history of injury, but in the military hospitals we find more cases of vascular spasm than you might appreciate.

We find cases of vascular spasm in the presence of nonpenetrating wounds. There is scarcely a small Station Hospital where I visit, where I cannot find one or more examples of mild or severe vasospasm. You will sometimes find it following a simple fracture of a long bone, and you will sometimes find very severe forms of vasospasm in the more severe wounds, the compound wounds of legs and arms accompanied by infection.

Leiche, twenty years ago, pointed out that vasospasm could be set up by a slight superficial infection, such as you might find between one's toes, and just a few weeks ago I found a patient in one of our hospitals with trichophytosis, and he had an extraordinarily severe degree of bilateral vasospasm, so severe on one foot that an ulcer of the soft tissues was present.

Colonel Elkin has referred to the importance of vasospasm in the severely wounded, and Major DeBakey recently has written a very excellent short article on vasospasm in war injuries published in "The Bulletin." Major DeBakey points out that vasospasm may be present when the penetrating wound is several centimeters away from the artery, and that a wound several centimeters from an artery may throw a major artery into complete spasm.

It is appreciated by the military personnel that vasospasm may shift the balance toward necrosis of soft tissues, that it is important to pay attention to vasospasm when it does complicate war injuries, those injuries where the major artery might be severed, or other injuries in which you have edema of tissues, or in which you have hematoma under the fascial planes which may produce pressure on whatever collateral blood supply is present.

And then, of course, the surgeon must pay attention to the kind of dressing that is applied to the wound, not to put it on too tightly, to be careful in the application of plaster encasements, and also in the use of tourniquets. Vasospasm can then turn the balance towards the production of necrosis of tissues. It is also believed that vasospasm can be a factor in the development of gas bacillus infections in the soft parts.

I would like to emphasize Colonel Elkin's fourth case by referring to it briefly. This patient received a severe injury of his left arm. The wound was treated by debridement. Then, about three weeks later, two aneurysms of the left arm were excised, one of the brachial artery and one of the ulnar artery, and subsequently, after about a week or ten days, the patient showed intermittent vasospasm of the left arm. He gave no history of vasospasm preceding the injury. Then, after another interval of a week or so, intermittent vasospasm appeared in the right arm, and subsequently in his legs, and then it spread to involve the trunk, the abdomen, chest, neck, face and ears, so that starting with the left arm vasospasm spread to involve the entire vascular tree.

Sympathectomy was undertaken on the left arm and gave a good result in that arm. I am curious to find out whether it had any effect in breaking the chain of events to the other three extremities.

I saw this patient. No doubt if the chain is not broken by the sympathectomy he may need sympathectomy in the other three extremities.

Colonel Elkin, in his paper, recommends injection by novocaine or sympathectomy in those patients where the viability of the soft tissues is threatened. But as I see patients in the General Hospitals who have suffered severe war injuries, I think perhaps the

operation of sympathectomy should be extended more commonly to those patients who have severe symptoms 'from vasospasm without necrosis. These symptoms may be very severe.

I think perhaps in the future sympathectomy may be applied more commonly to these patients.

DR J D RIVES, New Orleans, La. I do not wish to challenge Doctor Elkin's opinion that ligation and complete excision is the most generally useful method of treatment in traumatic arteriovenous fistula, but I do wish to call attention to the fact that there are many instances in which it is either impractical or undesirable, and that in such cases the several operations of Matas are still extremely valuable. Several individuals writing upon this subject in recent years have made it apparent that the principles underlying the Matas' operations are sometimes imperfectly understood. The obliterative aneurysmorrhaphy, whether it be applied to arterial or arteriovenous aneurysm, has as its chief advantage the fact that it requires a minimum of dissection and preserves all of the collateral circulation.

I would like to show you two slides illustrating this fact. This case is one operated upon by Dr Urban Maes, the arteriograms having been done by Dr Ross Veal. It is a popliteal arterial aneurysm, syphilitic in origin. The first slide demonstrates the fact that the two main openings into the sac lie superficial in the popliteal space but that the sac itself is deeply placed and that the collaterals lie immediately adjacent to it. The second slide shows the conditions after a typical intrasaccular suture by the Matas method. You will see that the largest collaterals emerge from the main trunk so close to the openings into the sac that it would be quite impossible to ligate the artery without destroying them. Furthermore, dissection of the sac would have destroyed numerous other collateral channels that have, by this method, been completely preserved.

The second case illustrates the application of this method to an arteriovenous aneurysm. This patient was a young colored male who had suffered a gunshot wound of the left thigh. A huge false aneurysmal sac developed, extending from Poupart's ligament and the pubis to about the junction of the middle and lower thirds of the thigh. It contained fully two liters of blood at the time of operation. Due to the location of this sac it was impossible to secure preliminary control of the circulation. It was at first thought to be a connection between the common femoral artery and the femoral vein, but proved at operation to involve the profunda femoris. The superficial femoral artery was stretched across its wall and practically collapsed by pressure. It was ligated due to an error that resulted from an anatomic anomaly. The external iliac artery bifurcated above Poupart's ligament and the superficial femoral and profunda femoris passed separately beneath Poupart's ligament. Since obliteration of the artery by compression caused marked diminution of pulsation and thrill in the sac, the superficial femoral artery and the femoral vein were ligated before the nature of the aneurysm was recognized. The profunda femoris lay directly beneath the superficial femoral artery. If an attempt had been made to dissect out this sac and ligate its various connecting vessels I would probably have lost the patient from hemorrhage, and I would certainly have destroyed all of the most important collateral circulation to the leg. By intrasaccular suture it was possible to close the seven openings into the sac and preserve an entirely adequate collateral circulation. The technical difficulties of this procedure I shall not discuss here but I am sure that it will be apparent to you that even the intrasaccular suture was far from a simple procedure.

The third case illustrates the usefulness of the reconstructive type of operation for direct arteriovenous fistula. This patient was a middle-aged colored male who had suffered a gunshot wound of the neck which resulted in the formation of a large direct communication between the common carotid artery and the internal jugular vein immediately below the bifurcation of the common carotid. He was a middle-aged

patient with damaged peripheral arteries and it seems to me apparent that under such circumstances the ideal procedure should include preservation of the common carotid artery. The transvenous suture of Matas is applicable only when it is possible to obtain complete preliminary control of circulation, which is obviously not feasible in the neck unless the artery and vein can be isolated on both sides of the communication. The proximal control in this instance was secured without great difficulty, but scarring above the fistula was so dense that every attempt to isolate the external and internal carotid arteries and the internal jugular vein resulted in active hemorrhage which could be controlled only by suture of the vein. Accordingly, the site of the arteriovenous communication was isolated and the fistula closed by means of two rows of interrupted U-sutures of silk. The vein was then obliterated by additional sutures which encircled its entire lumen. In this way, the artery was reconstructed and its function preserved. I believe that it is not only unnecessary but unwise to preserve the continuity of the involved vein because the venous collaterals are always adequate and the preservation of such a large vein after considerable trauma to its intima invites thrombosis and embolism. This operation is simply a variant of the Matas' transvenous suture, making it applicable when preliminary control of circulation cannot be accomplished. In this instance the ligation of all communications and excision of the fistula would have seriously impaired the cerebral circulation even if it could have been accomplished without undue risk. The reconstruction of the artery was not only better but easier.

I believe that these examples demonstrate the fact that the Matas operations are not obsolete. I am sure that Doctor Elkin is fully aware of these facts and probably has included them in the complete version of his paper. In the limited time it was necessary that he place his emphasis on the methods most generally useful in the type of cases seen in military hospitals. In young individuals with peripheral arteriovenous communications the collateral circulation is, I believe, always adequate, in most instances preliminary control of circulation is possible, and ligation and excision of the aneurysm is the surest and simplest method of treatment. This is unquestionably true in those aneurysms having numerous communications with a relatively small sac such as the three cirroid-type aneurysms that he has described. I wish to emphasize the fact that the surgeon who attacks arteriovenous aneurysms should be familiar with all of the various methods that have been described, any one of which he may be called upon to use in an individual instance, and that it is not infrequently necessary for him to improvise modifications or combinations of these procedures after the nature of the lesions has been demonstrated by dissection.

DR ALLEN O WHIPPLE, New York. I had not expected to discuss this paper, but a reference to the work that Doctors Blakemore and Lord have done in this field has not been mentioned, and it seems to me that it is only fair to speak of the original work they have done.

Blakemore and Lord have devised a nonsuture method of bridging gaps in main arterial defects, which in a large series of animal experimentations has proven remarkably effective, and has been used in a sufficiently large number of clinical cases to show that it is not only feasible but readily carried out.

I regret that I have not lantern slides to show that method, but the essential parts of it are that a vein graft is threaded through a vitallium tube on two ends, and the endothelial-covered vein ends are introduced into the ends of artery that have been excised or damaged. This endothelial-to-endothelial lining permits of a reestablishment of circulation through the artery, thrombosis does not result, and the restoration of circulation to the limb is promptly reestablished.

In the animal work which they have carried out, they have excised portions of the femoral, ligated the ends, and established an infected wound, and later, between 12 and 24 hours, have reestablished circulation in that limb by means of this technic.

I have used it myself in anastomosing the splenic vein to the renal vein in the case of portal obstruction, and the patient who had been having repeated gastric or esophageal hemorrhages, and had been tapped a number of times before the operation, has had no recurrence of bleeding or of ascites for nine months

I think Doctor Andrus, who has observed this work where it was done in the surgical laboratories of Cornell, has seen the animal work in this field, and it seems to me it is only fair to say that this is a method of reestablishing circulation in a main arterial trunk which must be considered and must be given due study and tried

In a series of eight cases that I saw in Bizerte last summer, seven of them had come to amputation (these were injuries to the popliteal artery) and they had all been previously treated with paravertebral block

DR VILRAY P BLAIR, St Louis, Mo Did that vein that substituted for a section of a large artery dilate? If it did not, why?

DOCTOR WHIPPLE All I can say is that a vein has been used to replace segments of the abdominal aorta, and an aneurysm has not resulted It is a very interesting example of Wolff's law, in that function apparently creates an hypertrophy and hyperplasia in the venous segment

LT COL ELKIN (closing) I am very glad to have Doctor Whipple bring to the attention of this Association Doctors Blakemore and Lord's work, which of course is of extreme importance Doctor Whipple will realize, however, that the patients which I reported here were seen anywhere from six weeks to six months after the origin of the injury, and the application of the principle at that time was hardly applicable

In the patient which Doctor Beck discussed, a sympathectomy has been done on the arm first involved, and that arm appears normal, as normal as a sympathectomized arm will, and there is improvement in the other extremities

I did not wish to leave the impression that complete excision of an arteriovenous aneurysm is always advisable or possible, but that many other methods, such as infolding or a transvenous closure, or some particular method devised at the moment, may be necessary in eradication of these lesions

# THE USE OF PENICILLIN IN SURGICAL INFECTIONS\*†

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THE IMPORTANCE OF PENICILLIN must be gauged in accordance with its relationship to previous methods of treating infection. After eight years of experience with sulfonamide chemotherapy of bacterial infections, it is appropriate to examine the present status of these drugs as they affect the practice of surgery and to determine to what extent penicillin gives promise of meeting the limitations of the sulfonamides. Convincing evidence of the value of sulfonamide therapy is to be found in contrasting the 38 per cent-case fatality rate from meningitis during World War I with the current Army rate of 4 per cent<sup>1</sup>. Similar comparisons could be made with respect to pneumonia and streptococcal sepsis. However, in considering special surgical infections separately from infectious diseases as a whole, we find that the sulfonamides possess certain very definite shortcomings which are of especial significance to the surgeon. By a "surgical" infection is meant a lesion which is fundamentally associated with a localized component in soft tissue, bone, or serous cavity, within which irreversible damage to tissue architecture is likely to occur as a result of bacterial activity, and which, under certain conditions, may be benefited by surgical treatment of the localized focus. For further discussion of the special characteristics of surgical infections see Meleney<sup>2</sup>. Sulfonamide therapy has modified the invasive aspects of many of these surgical infections, particularly those due to hemolytic streptococci, and, in a less striking degree, to staphylococci, and has thereby reduced mortality and increased the effectiveness of associated surgical treatment; furthermore, there is reason to believe that sulfonamides have improved the prognosis of patients with various types of peritonitis of mixed bacterial flora. However, the sulfonamides have almost completely failed to influence the localized foci of tissue necrosis once they have developed, and have been least effective in surgical infections produced by those organisms which, like the *Staphylococcus aureus*, are the most active destroyers of tissue. As reported by Doctor Frank Meleney<sup>3</sup> before this Association a year ago, carefully controlled clinical and laboratory studies have failed to support enthusiastic claims that systemic and/or local sulfonamide therapy have modified the incidence of localized suppuration in accidental wounds of soft

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\* Read before the American Surgical Association, May 3-4, 1944, Chicago, Ill

† This report is based on work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania

parts and bone, particularly if the wounds had been subjected to primary closure. In the presence of products of tissue breakdown bacteria are resistant not only to the concentrations of sulfonamides supplied in systemic therapy but are also resistant to the action of even locally applied sulfonamides. In this connection there is, as yet, little really clear-cut evidence that locally applied sulfonamides are of any practical value in the treatment of suppurating wounds (excepting only superficial lesions free of necrotic tissue) unless radical surgery is first performed, and in many such cases the surgical procedure alone might be adequate to eradicate the infection.<sup>4</sup>

Another factor seriously limiting the usefulness of the sulfonamides in surgical infections has been the incidence of toxic reactions, particularly those resulting from acquisition of drug hypersensitivity, and those affecting the hemopoietic system and the kidneys. These reactions have not been so frequently severe as to contraindicate sulfonamide therapy in conditions where they could be relied upon to have definite therapeutic value—but many conscientious surgeons have been reluctant to use sulfonamides in prophylaxis under conditions where the likelihood of serious infection is remote.

In view of these limitations in sulfonamide therapy as applied to surgical infections, it is only natural that the advent of penicillin as a practical therapeutic agent should have been received with interest by students in this field. Although it is not within the scope of this paper to present a complete review of the literature on penicillin, it seems desirable to present in broad outline the historical development of this remarkable drug.

It was shown by Alexander Fleming,<sup>5</sup> who discovered penicillin in 1929, that the drug was highly effective *in vitro* against staphylococci and other gram-positive organisms, and by Abraham, Chain, *et al.*,<sup>6</sup> that its activity was not seriously impaired in the presence of proteolytic products of infection. Since it is not inhibited by para aminobenzoic-acid and peptones, as the sulfonamides are, the action of penicillin appears to be different in character from that of the sulfonamides. The first reports on the administration of penicillin to patients, by the group at Oxford University led by Professor H. W. Florey, was published in 1941.<sup>6</sup> Although they were working with rather small amounts of the drug, their results in severe staphylococcic infections were definitely encouraging and lent justification to energetic efforts to increase the production of penicillin both in England and the United States. The large-scale production of the drug, derived from cultures of a certain strain of the mold *Penicillium notatum*, presented technical problems of an unprecedented nature, but as a result of the cooperative efforts of the British Medical Research Council, the Committee on Medical Research, the War Production Board, and several pharmaceutical houses both in Britain and the United States, and the laboratories of the U. S. Department of Agriculture in Peoria, Illinois, these problems have been successfully overcome, and the production of penicillin has now reached such a volume as to permit ample supplies for laboratory and clinical research. During the past fourteen months the Committee on Chemotherapeutics and Other Agents of the

National Research Council, acting for the Committee on Medical Research, has been responsible for the planning and execution of clinical research on penicillin, using supplies of the drug purchased from the manufacturers by the Office of Scientific Research and Development and allocated for civilian use by the War Production Board. As Chairman of this Committee, Doctor Chester S. Keefer has met urgent requests from civilian physicians for penicillin in treatment of severe sulfonamide-resistant infections in which penicillin therapy might be indicated.

For special research on surgical infections, penicillin has been provided to investigators working under the program of the Subcommittee on Infected Wounds and Burns, of the National Research Council, and to the Army and Navy. It is the purpose of this paper to present in rather general terms what has been learned by one of the participating groups regarding the scope and limitations of penicillin in surgical infections and to bring out the extent to which penicillin gives promise of meeting some important deficiencies of the sulfonamides through its effectiveness in the presence of pus, its powerful action against staphylococci, and its lack of toxicity. Among the few papers which have already been published on this subject is the significant report of Major Champ Lyons<sup>7</sup> on experience with penicillin in Army hospitals. Reports of general clinical studies on penicillin have been published by a number of investigators, including Abraham, Chain, Fletcher, Gardner, Heatley, Jennings and Florey,<sup>6</sup> Keefer, Blake, Marshall, Lockwood and Wood,<sup>8</sup> Dawson and Hobby,<sup>9</sup> Herrell,<sup>10</sup> and Bloomfield, Rantz and Kirby.<sup>11</sup>

TABLE I  
PENICILLIN SUSCEPTIBLE

*Gonococcus*  
*Meningococcus*  
*Str. hemolyticus*  
*Str. viridans*  
*Actinomyces bovis*

*Staph. aureus*  
*Staph. albus*  
*Cl. tetani*  
*Cl. welchii*  
*Cl. diphtheriae*

PENICILLIN RESISTANT

*Enterococcus*  
*Esch. coli*  
*B. typhosus*  
*B. paratyphosus*  
*B. dysenteriae*  
*H. influenzae*  
*H. pertussis*

*B. pestis*  
*B. proteus*  
*B. pyocyaneus*  
*B. Friedlander*  
*Brucella*  
*B. tuberculosis*  
*B. tularensis*

#### PROPERTIES OF PENICILLIN AS A CHEMOTHERAPEUTIC AGENT

Penicillin comes from the manufacturer in the form of the anhydrous sodium or calcium salt, varying in color from light yellow to deep reddish-brown. It is highly soluble in water, but tends to deteriorate in solution, particularly at room temperature or higher. In the anhydrous state it is fairly stable, and may be kept for several months without deterioration, particularly at refrigerator temperature. It is highly active *in vitro* against most gram-positive species of bacteria, including *Staphylococcus aureus* and *albus*, *Streptococcus hemolyticus*, and the *Clostridia*, and is also active against



the gonococcus and the meningococcus. The unit of penicillin is based on its activity *in vitro* and consists in the amount of the drug which must be added to 50 cc of broth in order to prevent the growth of a standard strain of *Staphylococcus aureus*. Therefore, one milligram of commercial penicillin, which contains on the average about 500 units of activity, would inhibit the growth of *Staphylococcus aureus* in 25 liters of culture media. Penicillin is not active against most types of gram-negative bacilli, including *Esch coli*, *B pyocyaneus* and *B proteus*, in fact the colon bacillus produces a substance, penicillinase,<sup>12</sup> which will rapidly destroy the activity of penicillin—a phenomenon of considerable importance in the practical treatment of surgical infections where this organism is present in mixed culture with gram-positive, susceptible organisms.

The mode of action of penicillin is still unknown. Strictly speaking, it is a bacteriostatic drug in that it apparently produces its effect on bacteria in the host by destroying their ability to multiply, once bacteria in the body cease to multiply and produce toxins they are rapidly destroyed by the antibacterial mechanisms of the host. Since the concentration required for this action is exceedingly small, about one-thousandth of a milligram of the pure drug per 100 cc of media, it is reasonable to believe that penicillin must exercise a highly selective effect on an enzyme system concerned in the process of bacterial growth. Its usefulness as a chemotherapeutic agent is a result of its ability to circulate throughout the body fluids in an active state and without producing any apparent toxic action on the cells of the host.

Penicillin must be administered parenterally, because it is inactivated by gastric juice and is not readily absorbed from the intestinal tract. It is rapidly excreted in the urine and in the bile, the rate of its excretion and the concentration in the blood depending upon the route of injection.<sup>13</sup> The highest blood concentrations and excretion rates occur with intravenous injection and the lowest with subcutaneous administration while the curves for intramuscular injections occupy an intermediate position. In practice, penicillin is usually given either by continuous intravenous drip, the 24-hour dose of drug being dissolved in the amount of normal saline or glucose which the patient can be given intravenously during this period, or in repeated intramuscular injections at intervals of two, three, or four hours, depending upon the intensiveness of treatment required. At this period in the development of penicillin, when the supply is limited, it is perhaps fortunate that the drug must be given parenterally, and, therefore, usually in hospitals, because, apart from existing legal restrictions this provides the only effective brake on the indiscriminate use of penicillin for all sorts of minor conditions.

The dosage of penicillin in various types of infections is not yet standardized. Emphasis has necessarily been placed upon determination of minimal effective doses for different types of infections because of the scarcity of the drug, but the almost complete lack of toxicity of penicillin has permitted considerable latitude in pushing dosage upward when smaller doses are ineffective. Most cases of gonorrhea will, for example, respond to

10,000 units every three hours for five doses, a total of 50,000 units. However, in cases of severe staphylococcal bacteremia, the average dose of 120,000 units per day for ten days may at times be increased to 300,000 or 400,000 units per day for a similar period. Increasing systemic dosage beyond this point will probably result only in waste of the drug. Duration of treatment, of course, depends upon the clinical response of the individual case, upon the timing and feasibility of associated surgical procedures designed to remove penicillin-resistant foci such as bone sequestra, and, finally, upon clinical judgment in respect to the likelihood of relapse in the type of infection being treated. Much more experience will be required before definitive rules can be provided in these matters of dosage and duration of treatment.<sup>7</sup>

#### LOCAL USE OF PENICILLIN

There are a number of conditions in which it appears to be desirable to use local penicillin either in conjunction with systemic therapy or by itself. It happens that penicillin is not readily permeable through serous and endothelial membranes, including the so-called "blood-brain barrier," therefore, it is usual practice in treatment of meningitis to inject about 10,000 units once or twice daily into the lumbar canal or the cisterna. In a similar way penicillin may be injected into empyema cavities and infected joints into which the passage of penicillin from the blood is usually quite limited, the high local concentrations produced by this method probably aid in causing disappearance of the infecting organisms, but will not necessarily render surgical drainage unnecessary in chronic cases if the cavity is thick-walled and contains large masses of heavily infected fibrin. Penicillin solutions containing 50 to 250 units per cc. may be used for semi-continuous irrigation of contaminated or infected wounds and are especially useful, in our experience, in the postoperative management of wounds incident to sequestrectomies for chronic osteomyelitis.

Studies now in progress under the auspices of the Committee on Medical Research should develop the possibilities of penicillin in various vehicles for local treatment of wounds, as yet, our own clinical experience with these preparations has been inadequate to justify any definite statements other than that the results are highly encouraging. However, Florey and Williams<sup>14</sup> have reported a controlled series of 110 minor surgical infections of the hand in which the results of local penicillin treatment as an adjunct to surgical therapy were compared with 102 control cases treated by standard methods. Among 35 pulp and tendon sheath infections, alone, the saving of working time attributable to penicillin was 1000 days! "In the penicillin treated series, given adequate access and removal of dead tissue, sepsis by clinical and bacteriologic criteria was eliminated within a week." The total amount of penicillin used to treat over 100 cases locally was less than 500,000 units, which is a minimal dosage for *systemic* treatment of one case of severe sepsis. Another group<sup>15</sup> in Britain have found an ointment containing penicillin to be useful in shortening the healing time of infected superficial

burns Garrod<sup>16</sup> has written on the prophylaxis and treatment of war wounds with penicillin

#### LABORATORY STUDIES

One fact which has stood out as of paramount importance in the effective utilization of penicillin has been the necessity for careful bacteriologic study of every case in which the drug is used. In the first place, one must know whether or not the causative organism is susceptible, because occasional resistant strains of staphylococci or streptococci are encountered which will require more intensive treatment. Determination of sensitivity of an organism to penicillin can be performed by a simple procedure adaptable to any bacteriology laboratory.<sup>6</sup> In the second place, it is important to identify the presence of penicillin-resistant species such as *Esch coli*, or *B pyocyaneus* or *B proteus*, although not highly parasitic in wounds when in pure culture, these types of bacteria are not only resistant to ordinary concentrations of penicillin but as previously mentioned, some of them elaborate a "penicillinase" which rapidly destroys penicillin and may interfere with the action of the drug on penicillin-susceptible species which are present in the wound. Finally, frequent examination of the bacterial flora of the exudate in a localized infection, or the blood in a case of bacteremia, is the best method of determining the adequacy of treatment in any individual patient, and may be employed in determining the optimal time for surgical intervention in cases of chronic osteomyelitis with draining sinuses or in determining a favorable time for secondary suture.

Determination of the concentration of penicillin in the blood and body fluids is a procedure requiring some special laboratory facilities and technical skill,<sup>17</sup> and, though important to the conduct of research on penicillin, will probably not be essential to the routine practical use of the drug in treatment of infections. In this respect penicillin differs greatly from sulfonamides because excessive blood levels of penicillin are simply wasteful and not actually dangerous to the patient. Determination of susceptibility of the organism to penicillin and of the clinical and bacteriologic response of the patient are adequate practical guides to the administration of this drug. It goes without saying that in using penicillin in the treatment of acute and chronic infections one must not lose sight of the importance of other aspects of therapy, such as maintenance of adequate nutrition, correction of anemia of the results of many investigators will be of far greater significance than ment of wounds. These considerations have been well emphasized by Lyons.<sup>7</sup>

#### RESULTS OF PENICILLIN IN SURGICAL INFECTIONS

During the past 18 months our penicillin research unit at the University of Pennsylvania has been privileged to treat about 440 patients, not only in our own hospitals, but also in many other institutions in Philadelphia. In some of these cases the entire clinical management has been in our hands, but in many we have served only as a distributing agency for supplying the

drug after having satisfied ourselves as to the suitability of the case for penicillin treatment. In all cases the opportunity has been given to us of regulating dosage and laboratory studies, making frequent examination of the patients, and preparing special research records. The diseases treated have been of many varieties—both medical and surgical, and except for special research cases of chronic osteomyelitis and pulmonary suppuration, all of them were critically ill. Most of them had received intensive sulfonamide treatment without success for periods of two days to several weeks. As a rule, the request for penicillin was not made by the attending surgeon or physician until other available measures had failed to effect a cure, and, with only limited amounts of penicillin available, we were disposed to treat only such cases as had failed to respond to other therapeutic measures. This has made it possible for us to study severe infections in all stages of development, from very early lesions to very advanced ones. Because of the wide scope of this study we have chosen to avoid any attempt at a presentation of our detailed statistics at this time. The statistics to be published later through a pooling of the results of many investigators will be of far greater significance than those from any one unit. Instead, we propose in this paper to discuss in a general way, the results of penicillin therapy in several broad categories of surgical infections—introducing selected case summaries to illustrate the bases for the conclusions which we feel permitted to make. The four main groups to be discussed are acute disseminated sepsis, and localized infections of serous cavities, soft tissues, and bone, respectively.

#### ACUTE DISSEMINATED SEPSIS (BACTERIA AND MENINGITIS)

Included in this group were 57 cases of staphylococcic bacteriemia of which two-thirds survived, 15 cases of streptococcic bacteriemia and 50 cases of suppurative meningitis, of which 43 were pneumococcic and 5 staphylococcic. The cases of staphylococcic bacteriemia probably illustrate better than any others the important position of penicillin as a chemotherapeutic agent. Whenever possible these cases were treated by the continuous intravenous drip method and received doses of 60,000 units to 150,000 units in each 24-hour period. With impressive regularity these patients tended to show improvement within 48 hours and, unless complications had developed, were clinically recovered from the acute disease within three to seven days. The complication most likely to interfere with successful treatment was vegetative endocarditis, which developed in ten cases. In most of these bacteriemia cases no resort was made to surgical treatment of foci of localization during the acute septic phase of the infection because in the face of progressive improvement in the patient's condition it seemed wise to defer operative procedures until a time of election. In several instances the foci of localization subsided without requiring drainage, particularly those developing in well vascularized tissues about the face, and in the lung. When localization in bone occurred it has usually been necessary to resort, ultimately, to surgical drainage. This will be discussed later as a special topic.

Case 1—H E (Fig 1) *Diagnosis* Cavernous sinus thrombosis *Staphylococcus aureus* bacteriemia

A 35-year-old Negro developed swelling of eyelids and fever two days following a severe blow on the nose. On admission to the Pennsylvania Hospital, March 6, 1943, he was acutely ill, showed chemosis and proptosis, with engorgement of veins and ophthalmoplegia on the left side. Blood culture was positive for *hemolytic Staphylococcus aureus*. The same organism was present in purulent drainage from the right eye. After failure to respond to sulfadiazine for 48 hours he was given penicillin intravenously. Heparin and dicoumarin were given to prevent propagation of thrombi. His response to the treatment was very satisfactory. Temperature became normal in four days. The local signs subsided progressively. He was discharged, well, on April 25, 1943.

Case 2—B C (Fig 2) *Diagnosis* *Staphylococcus aureus* bacteriemia, questionable acute endocarditis

An 11-year-old boy entered the Hospital of the University of Pennsylvania, May 26, 1943, during the third week of an acute illness characterized by fever of 104° to

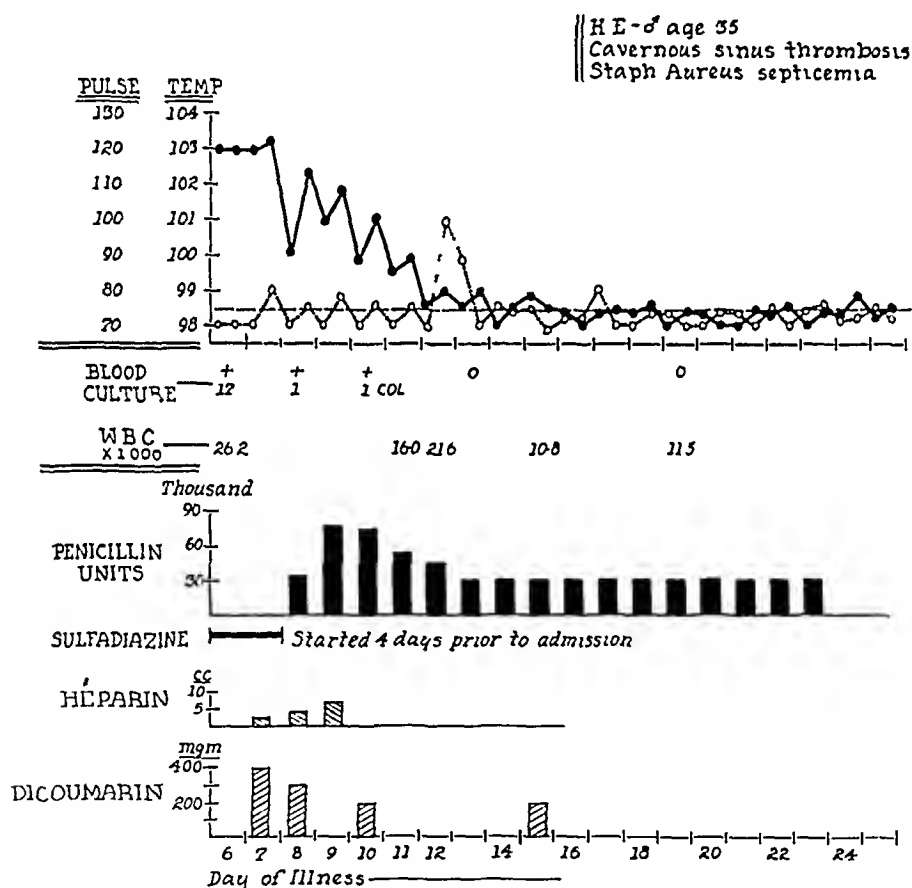


Fig 1

106° F, headache, and delirium. He had received sulfathiazole and sulfadiazine without apparent benefit. The day before admission petechiae had appeared on the extremities, and soon appeared in conjunctivae and mucous membranes as well. Blood culture was positive for *hemolytic Staphylococcus aureus*. Penicillin was started by intravenous drip in doses of 100,000 units daily. Blood culture remained positive for two days, spleen became palpable and tender, and a rough systolic murmur appeared, justifying a diagnosis of acute vegetative endocarditis. Spiking fever continued in spite of the

## PENICILLIN

development of negative blood cultures. On June 6, when the temperature reached 106° F, it was decided in desperation to try combining sulfadiazine with penicillin. Prompt and progressive improvement followed. Within a week the temperature had reached near-normal levels, the heart murmur disappeared, and the patient appeared to be convalescing. There were some febrile episodes in his course thereafter, the most alarming being associated with unexplained meningismus and pleocytosis of the

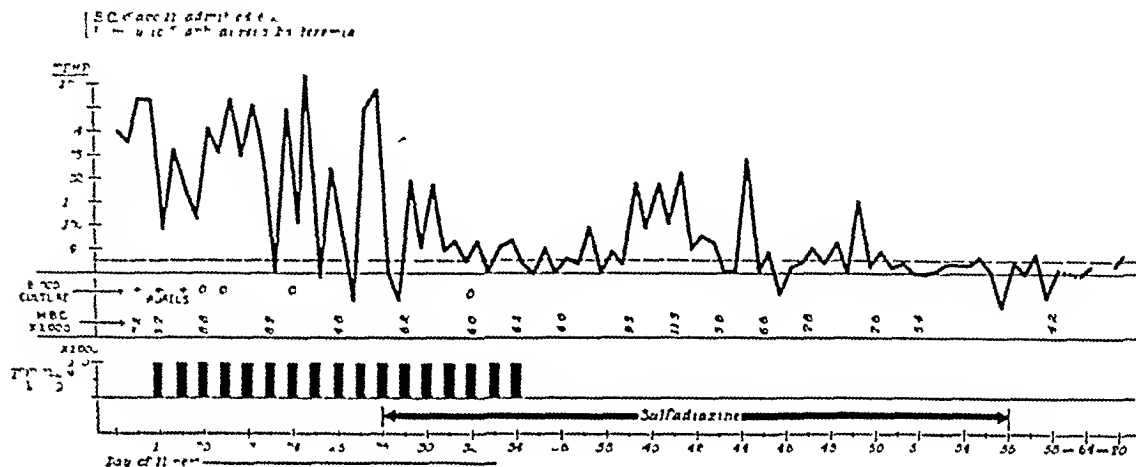


Fig 2

DM # age 6  
Osteomyelitis left Femur

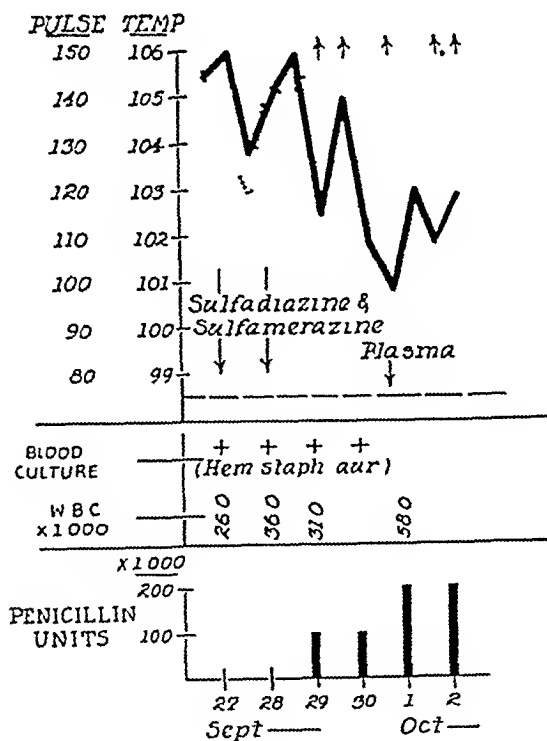


Fig 3

cerebrospinal fluid, but there was no recurrence of staphylococcic sepsis. He was finally discharged in good condition on July 18. At no time did he develop any lesions requiring surgical drainage. The primary focus of his infection remained indeterminate.

This case apparently represents a recovery from acute staphylococcic endocarditis, a complication which has seemed usually to be fatal in spite of penicillin. The clinical

evidence of the value of combined therapy with sulfonamides and penicillin tends to confirm laboratory studies on this point

**Case 3—D M (Fig 3)** *Diagnosis Staphylococcus aureus bacteriemia and meningitis*

A six-year-old white girl came into the Jewish Hospital, September 27, 1943, three days after acute onset of pain in the left hip and thigh. Her temperature was fluctuating between 105° and 107° F. A diagnosis was made of acute osteomyelitis of the left femur, with *Staphylococcus aureus* bacteriemia. Petechiae appeared, but without other evidence of endocarditis. Penicillin was commenced on September 29, 1943, and continued for two days at 100,000 units per day, and for one day at 200,000 units. In spite of these doses, which were large for a child of her age, the bacteriemia persisted, she showed no evidence of response to treatment and died October 2, 1943.

Autopsy disclosed widespread staphylococcus infection involving meninges, lungs, kidneys, left femur and left knee joint. Laboratory studies revealed that the inhibiting concentration of penicillin for this organism was *four hundred times* the usual level for *Staphylococcus aureus*. This fact explained the fatal outcome.

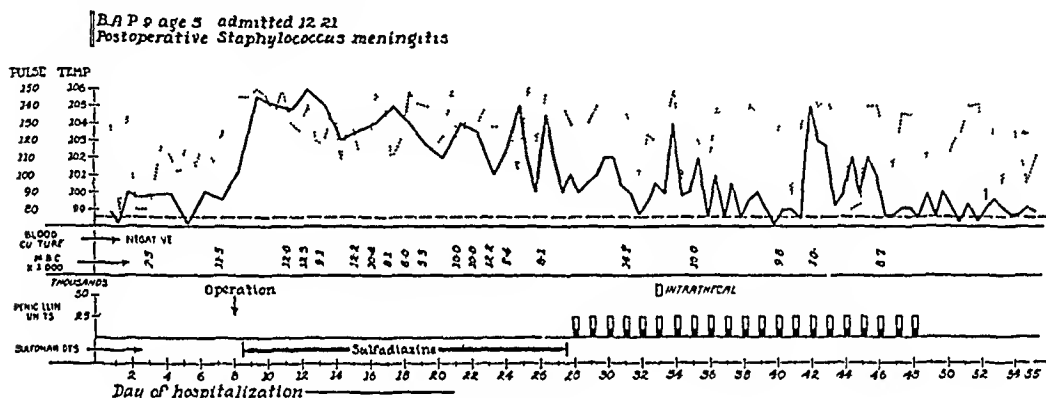


Fig 4

Meningitis, with or without bacteriemia, has continued to present major problems in management. Some of the cases, particularly those due to staphylococci, have responded rather promptly, even at times without intrathecal treatment, but the patients with pneumococcal infection have, in our experience, required especially energetic treatment, and the majority have died, nevertheless. As a rule, it was possible to obtain a marked bacteriologic response in these cases, the blood stream and spinal fluid showing either marked reduction in numbers of bacteria or even frank sterilization, but with the patient then succumbing either to hydrocephalus from mechanical block of spinal fluid drainage, from an acute toxic encephalitis, or from bacterial endocarditis. In cases of pneumococcal meningitis we feel that a daily injection of about 10,000 units of penicillin into the lumbar canal, cistern, or ventricles is imperative—and recent experiences suggest that the cisterna injections are particularly advantageous in severe infections. In meningitis it remains a matter of great importance to explore potentially infected mastoids in cases where a prompt clinical response is not forthcoming.

**Case 4—B A P (Fig 4) *Diagnosis* Postoperative *Staphylococcus aureus* meningitis**

Following operation, December 28, 1943, for cerebellar tumor this three-year-old child developed an acute *Staphylococcus aureus* meningitis. Treatment for 18 days with sulfadiazine failed to relieve the infection and spinal fluid cultures remained positive. Penicillin was started systemically and intrathecally on the 19th day and continued for three weeks. Spinal fluid cultures became negative after the first day of treatment and remained so thereafter. One week after completion of penicillin treatment she was discharged in good condition.

**Case 5—D K (Fig 5) *Diagnosis* Pneumococcic meningitis following mastoiditis**

This two and one-half-year-old baby was admitted to the service of Dr. William Atlee, Lancaster, Penna. General Hospital, February 9, 1944. He was acutely ill and stuporous with pneumococcic (Type XIV) meningitis secondary to acute otitis and mastoiditis. During the first four days sulfadiazine and specific antiserum were admin-

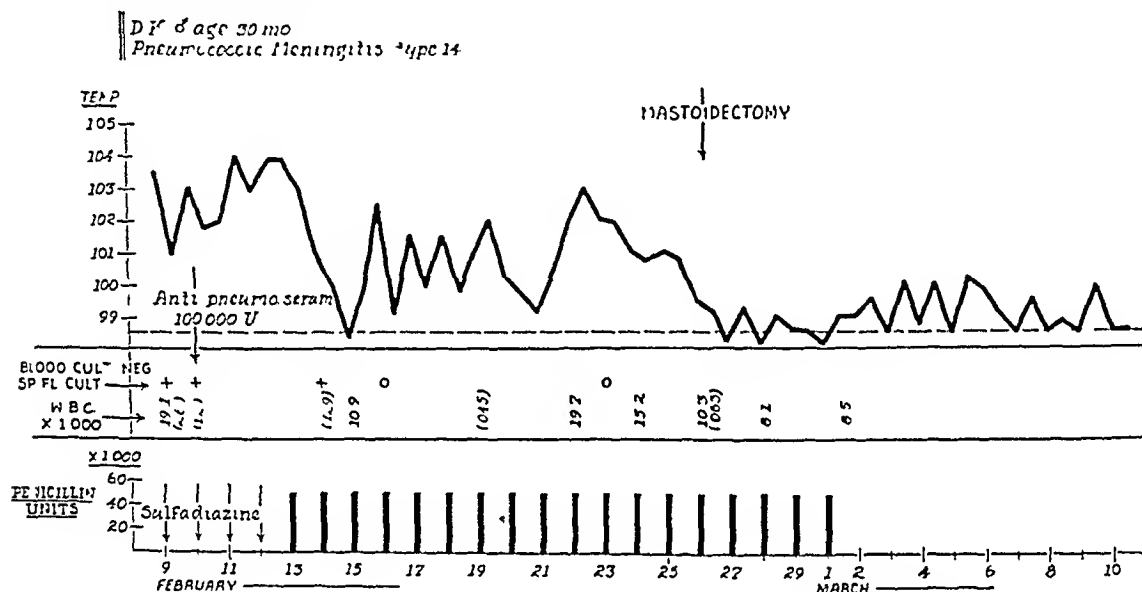


Fig. 5.

istered, without improvement, stupor remained and right hemiplegia and nystagmus appeared. Penicillin in doses of 50,000 units daily intramuscularly was started on February 13, and 5,000 units were given daily into the cisterna. Within four days marked improvement had occurred. Negative cultures of spinal fluid were obtained on February 16. The temperature rose again on the 22nd and 23rd, when penicillin was given by lumbar, instead of cisterna, puncture, but spinal fluid culture remained negative. On February 26 a radical mastoidectomy was performed. Five days later the penicillin was stopped. The mastoid wound healed uneventfully. He gradually recovered from the paralysis, and by March 24 was able to walk.

This case represents a recovery from meningitis of extreme severity. It illustrates the importance of intrathecal penicillin, the possible superiority of cisternal lumbar injections, and the need for surgical drainage of primary foci.

Of the 44 cases of pneumococcic meningitis which we have treated only eleven have recovered, and three of these are hopeless "spastics." All of the five cases of staphylococcic meningitis recovered. It is probable that through increasing experience with the use of penicillin in these cases, and



with more frequent employment of intracisternal treatment, recovery in a considerably larger proportion of patients with this disease may be obtained. Penicillin is quite adequate to deal with the pneumococcus when intimate contact of bacteria and drug can be effected.

#### LOCALIZED INFECTIONS IN SEROUS CAVITIES

*A Empyema* When the empyema is due to an infection with a penicillin-sensitive pneumococcus, staphylococcus, or streptococcus, in pure culture, and treatment is instituted within the first few weeks, it is possible to bring

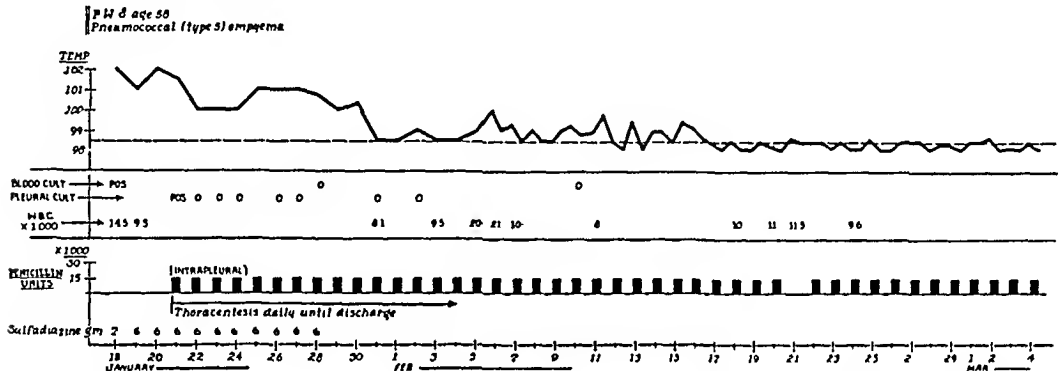


Fig 6

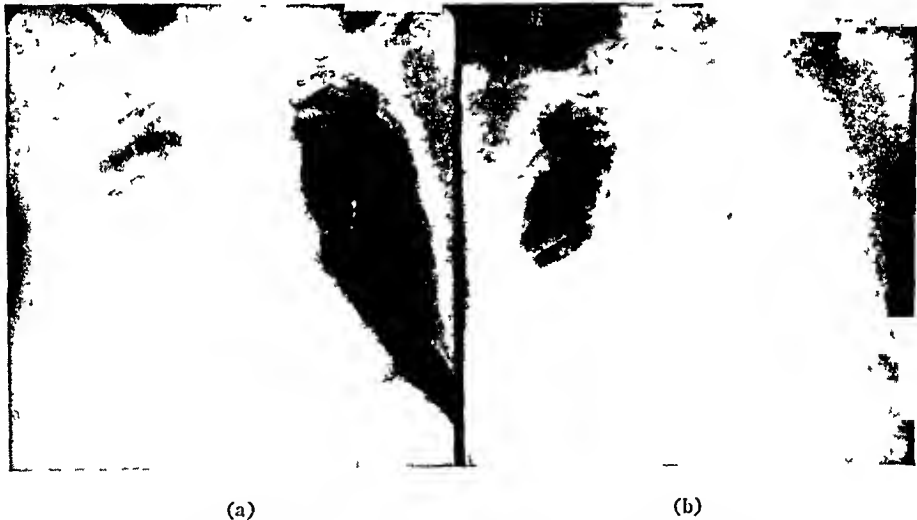


Fig 7—P W Pneumococcal (type 5) Empyema (a) X ray on admission to hospital (b) X ray 13 days after penicillin treatment was started

about sterilization of the cavity, and ultimate cure, without resorting to thoracotomy drainage. We have seen this accomplished in 19 cases through frequent aspiration of the cavity and injection of 10,000 to 25,000 units of the drug. If the patient is acutely ill, or shows other evidence of continuing parenchymal infection in the lung it is necessary to use systemic treatment in combination with the local injections. Failure to obtain a satisfactory bacteriologic and clinical response after two or three weeks of treatment will, of course, demand a resort to rib resection, but convalescence is shortened when this can be avoided.

**Case 6—P W** (Figs 6, 7 and 8) *Diagnosis* Pneumococcic empyema

This 58-year-old, white male, entered the Jefferson Hospital, January 18, 1944, on the fifth day of an attack of pneumococcic lobar pneumonia. Blood culture was positive



FIG 8—P W Pneumococcal (type 5) Empyema (a) X ray 26 days after penicillin treatment was started (b) X ray 1 month after discharge

for Type V pneumococcus. He received sulfadiazine from admission until January 29. Aspiration of the chest on January 20 revealed thick, green pus, culture again showed Type V pneumococcus. The patient was treated with daily aspirations of pus and injection of 18,000 units of penicillin from January 21 to March 4. Cultures of the

BS ♂ age 9  
Empyema

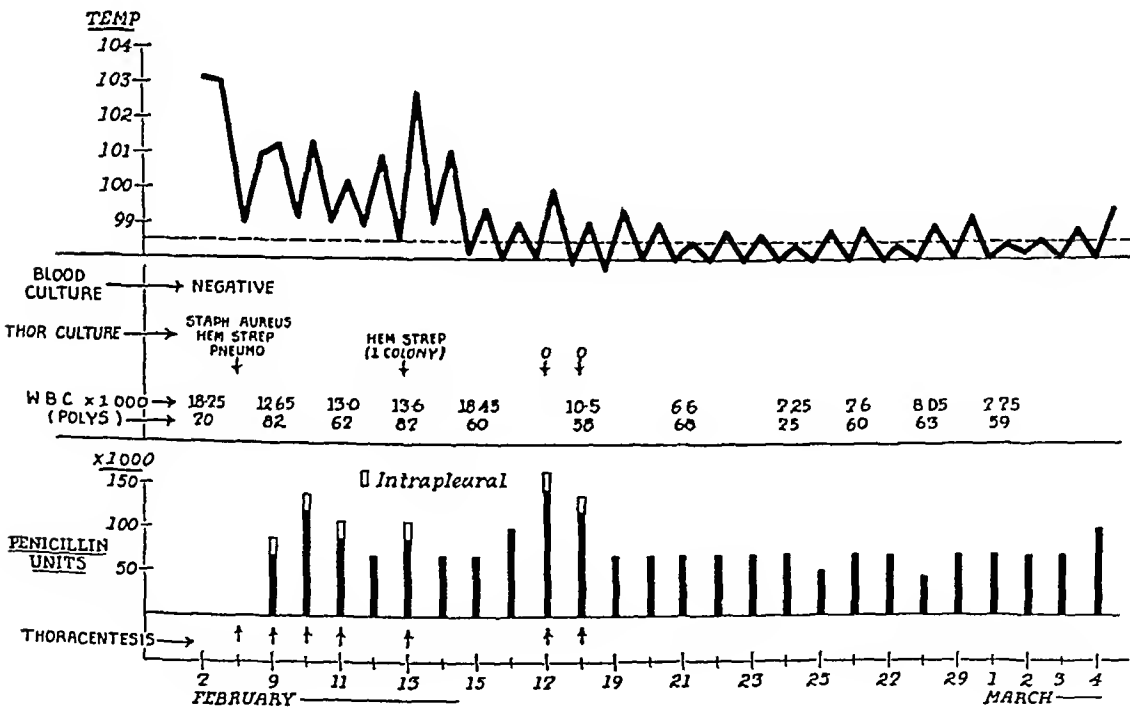


Fig 9.

empyema fluid were negative after the first injection of penicillin and remained so thereafter except for one positive culture on January 31. He was discharged, March 4, 1944, and has remained well subsequently.

Case 7—B S (Figs 9, 10, 11, 12 and 13) Diagnosis Empyema, polymicrobial.

This nine-year-old boy entered the Woman's Medical College Hospital, February 7, 1944, because of empyema which had developed following pneumonia treated with sulfadiazine five weeks before. Aspiration on February 8, 1944, showed 50 cc of thick creamy pus, containing *Staphylococcus aureus*, *Streptococcus hemolyticus* and *Pneumococcus*. Penicillin was given systemically from February 9 to March 4, a total of 1,875,000 units. In addition, aspiration of pus and injection of 20,000 units of penicillin was performed on six occasions between February 9 and February 18. The culture on February 13, after four days of penicillin, showed only one colony of hemolytic



FIG 10—B B Empyema—X ray of chest 2nd day of penicillin treatment

streptococcus, and subsequent cultures were sterile. The child's condition showed a parallel improvement, and by March 3 the empyema cavity was completely obliterated. He was discharged March 10, 1944, with evidence of slight pleural thickening, but otherwise in good condition.

This presents a good response in a mixed infection, but all of the organisms were sensitive to penicillin.

It should be observed that almost all current cases of empyema have had sulfonamide therapy, which has certainly modified the severity of the disease, and even brought about cure in many early cases, without need for surgical drainage. From our experience in the 34 cases of pneumococcal empyema, we are inclined to feel that treatment according to the plan carried out in the above case, without systemic penicillin, will permit avoidance of surgical drainage in perhaps the majority of cases when the empyema is unilocular. A single daily injection is sufficient to maintain a high concentration of penicillin in the pleural cavity. Of course, this treatment will be ineffective when the cavity is multilocular unless each pocket is dealt with separately.



FIG 11—B B Empyema—X ray of chest 6th day of penicillin treatment

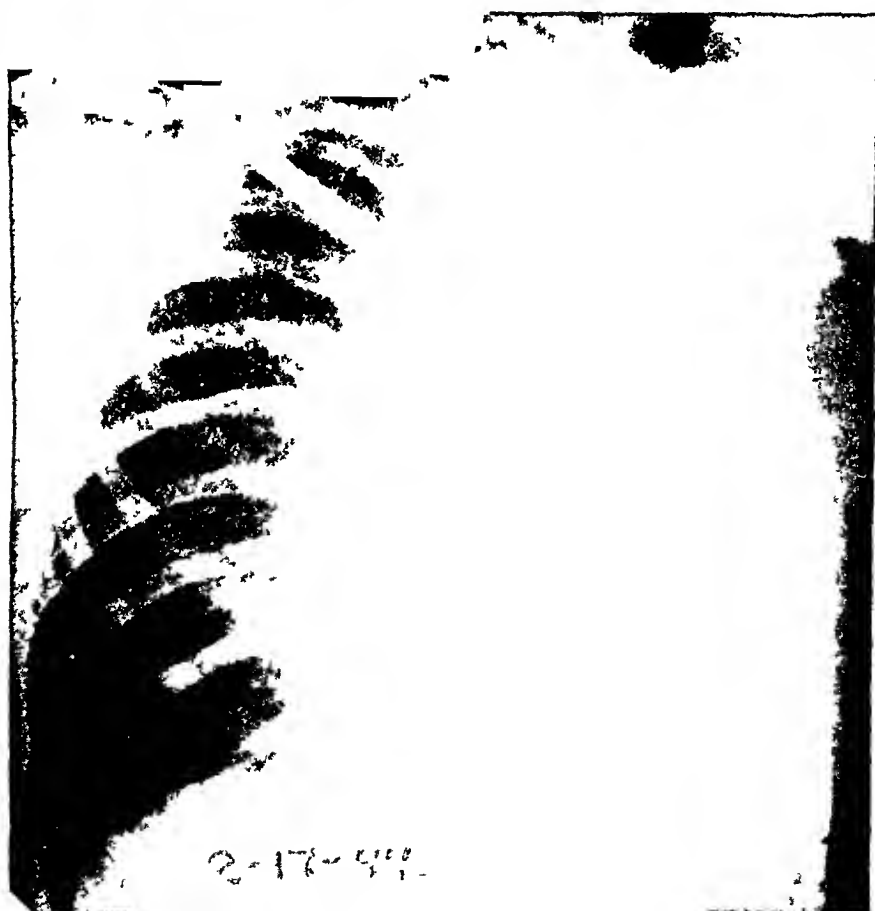


FIG 12—B B Empyema—X ray of chest 9th day of penicillin treatment

B *Suppurative Arthritis* What has been said in regard to empyema tends also to apply to suppurative arthritis. Complete restoration of function after staphylococcic arthritis has occurred in several cases.

**Case 8—E R** *Diagnosis* Arthritis of knee due to *Staphylococcus aureus*

A 33-year-old male came in for treatment of a chronic infection of the right suprapatellar bursa and knee joint. He had had an amputation of his left leg seven years before because of recurrent osteomyelitis. The present lesion was associated with a persistent infection in the lower end of the right femur which had been draining



FIG 13—B B Empyema—Follow up X ray 2 weeks after discharge

almost continuously for two and one-half years. At the time of an episode of active infection in June, 1943, the right knee joint had become infected with frank pus, and the surgeon who was taking care of him at that time inserted through-and-through drainage with rubber dam across the suprapatellar bursa. When he entered the Hospital of the University of Pennsylvania, November 17, 1943, he had been carrying this drain through his knee joint for more than four months. The infection in the femur was quiescent, but large quantities of pus were pouring from the drainage wounds of the joint. Culture showed *hemolytic Staphylococcus aureus* and diphtheroids. Penicillin, 100,000 units per day intramuscularly, was started on November 18 and continued until November 27, by which time drainage had practically ceased and culture showed only diphtheroids. On that day he was operated upon—the scarred sinuses were excised down to the thickened synovia and two small catheters were introduced. Systemic penicillin was continued and, in addition, 1,800 units of dilute penicillin was injected through the catheters every six hours. After one week, the cultures having remained sterile, the catheters were removed and two days later the systemic drug was discontinued. Active motion of the joint was then commenced. Infection did not recur, though straw-colored fluid free of staphylococci continued to drain intermittently for

several weeks. By February 1, 1944, his wounds were entirely healed. He was reexamined March 3, 1944, when his knee showed full range of motion. He is now back at regular work, entirely free of symptoms.

This case illustrates the remarkable recuperative power of chronically infected synovial tissue when active infection is eliminated with penicillin.

**Case 9—H S** *Diagnosis* Suppurative arthritis of ankle due to *Staphylococcus aureus*

A 64-year-old white male developed a suppurative arthritis of the ankle and was admitted to the Pennsylvania Hospital, April 14, 1943, the fifth day of disease. He showed only moderate systemic reaction but aspirated joint fluid showed pure culture of *Staphylococcus aureus*. The culture remained positive after four days of sulfadiazine therapy. Penicillin was given in doses of 100,000 units daily for one week, and at 50,000 units daily for nine additional days. On the fourth day of penicillin treatment, the joint fluid became sterile and remained so. After a period of treatment of carious teeth he was discharged with a normally functioning ankle joint on June 18, 1943.

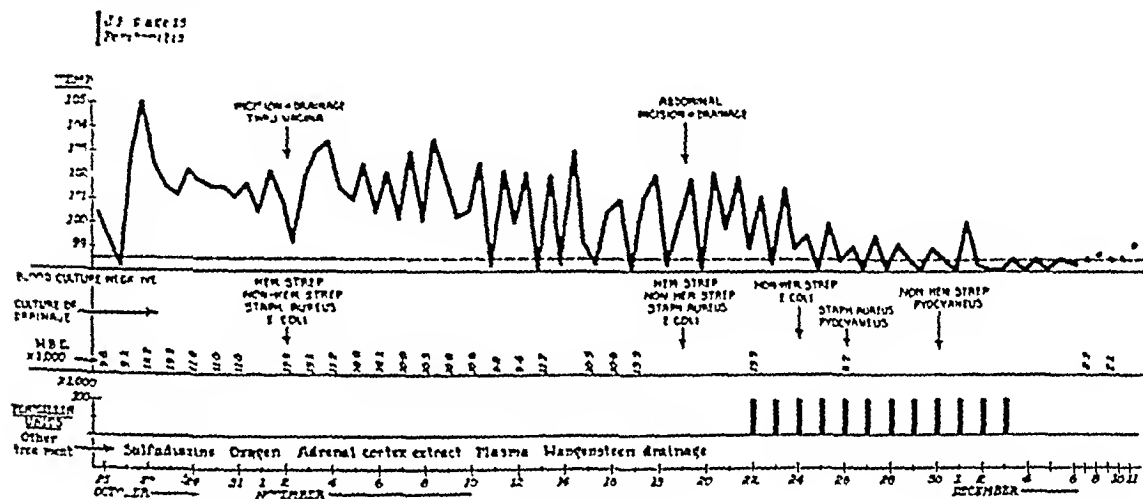


Fig 14

It is worthy of note that this patient received no local treatment of the infected joint other than aspiration. He would probably have recovered more rapidly if penicillin had been administered by injection into the joint.

**C Peritonitis** It has been possible to study only a few cases of peritonitis—partly because the limited supply of the drug has been inconsistent with treatment of infections in which penicillin-resistant organisms predominate, and partly because of the difficulty of evaluating the influence of a chemotherapeutic agent in lesions where there is considerable likelihood of recovery without the drug. Certainly, the cases of primary peritonitis from hemolytic streptococcal or pneumococcal infection would be expected to respond favorably to penicillin treatment. Less certain would be the results in treatment of infection developing after appendicitis, including pylephlebitis and perihepatic infections. However, some encouragement is to be found in cases such as the following.

**Case 10—J N** (Fig 14) *Diagnosis* Diffuse peritonitis, polymicrobial

This 15-year-old girl came in in shock and with paralytic ileus from appendical peritonitis which appeared clinically to be of generalized extent. She was given sulfadiazine,

plasma, Wangenstein suction, and oxygen. After a stormy week she developed a pelvic abscess which pointed in the vagina and was drained. Some improvement followed, including return of peristalsis, but elevated temperature, pulse and respirations persisted and her condition appeared critical. Blood cultures were negative. Another abscess was drained through a McBurney incision, November 19, 1943, but no improvement resulted. The pus from both abscesses showed hemolytic and nonhemolytic streptococci, *Staphylococcus aureus* and *E. coli*, and the second abscess showed *Cl. welchii* in addition. On November 22 penicillin in daily dose of 120,000 units was started intramuscularly at two-hour intervals. On November 24 her temperature remained for the first time at near normal levels and she began to feel much better. Culture showed disappearance of hemolytic streptococci. By November 26 only the nonhemolytic streptococci were present in the wound. Penicillin was continued until December 4, until normal temperature had remained for one week. She was discharged on December 12, but returned for uncomplicated appendicectomy in March, 1944.

In this case it appeared that the severity of the illness was attributable to hemolytic streptococcal infection. Once this organism was eliminated with penicillin she improved very rapidly.

**Case 11—E B (Fig 15) Diagnosis** Acute suppurative pancreatitis

After severe upper abdominal pain and nausea of eight days duration, this 33-year-old white female showed a sharp rise of temperature to 105° F, WBC of 33,000, and

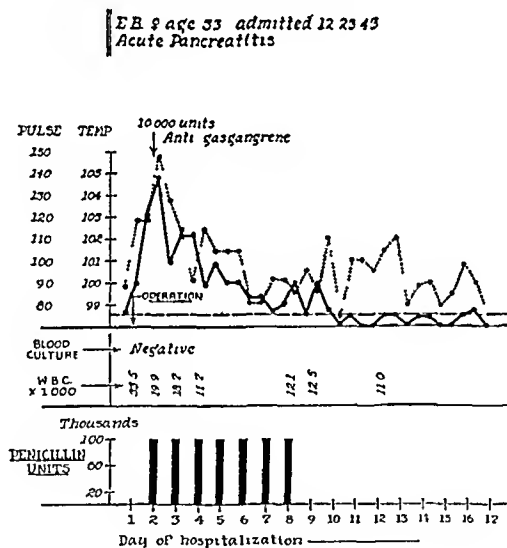


Fig 15

was operated upon for acute pancreatitis. Culture of the inflamed pancreas showed *Cl. welchii* and hemolytic *Staphylococcus aureus*. Cholecystostomy and drainage of the pancreas were performed by Dr J E Rhoads. The following day, when bacteriologic report was available, she was given 10,000 units of polyvalent antigas gangrene serum and started on 100,000 units of penicillin per day by continuous intravenous infusion. Rapid and progressive improvement followed, as shown in the chart, and she was discharged on the 16th day.

Certainly, there would be no justification for suggesting any modification in the indications for surgical intervention in cases of appendicitis, cholecystitis and peritonitis. Good results should be hoped for only in occasional cases

selected for penicillin treatment on the basis of careful bacteriologic examination

LOCALIZED INFECTIONS IN SOFT TISSUES

*A Cellulitis of the Face and Orbit* Particularly striking have been the results of treatment in patients with cellulitis of the face and periorbital tissues. The recuperative power of these well vascularized areas is illus-



Fig 16—A M S Orbital cellulitis

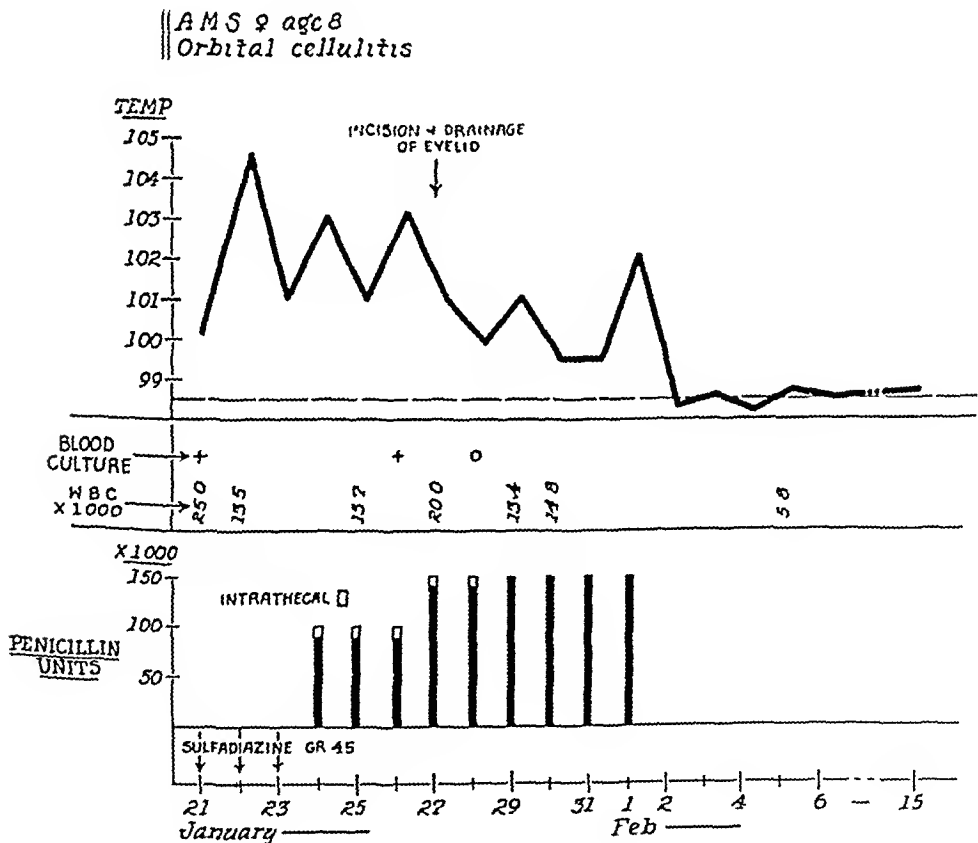


Fig 17

trated by the frequency with which penicillin treatment has been sufficiently effective to prevent suppuration in areas of facial cellulitis (Refer to Case 1)



Case 12—A S (Figs 16 and 17) *Diagnosis* Orbital cellulitis

This eight-year-old girl developed furunculosis of the right lower eyelid, and was admitted in stuporous condition to the service of Dr William Atlee, St Joseph's Hospital, Lancaster, Pa., January 21, 1944. In spite of sulfadiazine she developed bronchopneumonia and meningitis, but with sterile cultures. On January 24 the blood culture showed *Staphylococcus citreus* and there was evidence of spreading infection. Penicillin was started intravenously at 100,000 units per day, and 10,000 units were administered daily by lumbar puncture. After two days the dose of systemic penicillin was increased to 150,000 units because the blood culture was still positive. By January 27 the lesion of the right eyelid had localized sufficiently to permit incision and drainage. Culture showed *Staphylococcus albus*. At the same time the ethmoid plate was curetted and

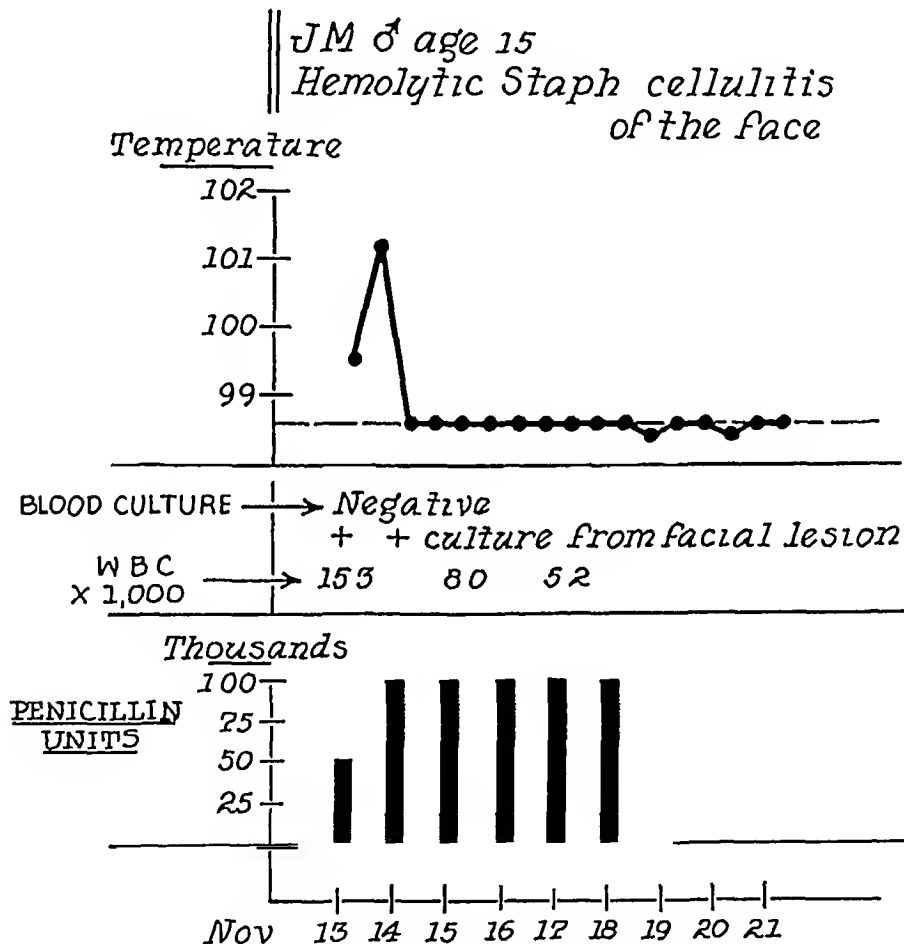


Fig 18

found to be infected. Her subsequent recovery was uneventful. Penicillin was discontinued on February 1, and she went home two weeks later with the drainage wound of the eye completely healed.

Case 13—J M (Fig 18) *Diagnosis* Cellulitis of the face, *Staphylococcus aureus*

A 15-year-old school boy developed cellulitis of the upper lip following severe trauma, and was admitted to the Hospital of the University of Pennsylvania, November 13, 1943, under care of Dr T Grier Miller. The entire right cheek was involved and both eyelids were swollen. Culture of the lip wound showed hemolytic *Staphylococcus aureus*. After 24 hours of penicillin, at 100,000 units per day, his temperature became normal. Regression of the cellulitis took place rapidly, and the patient was discharged on the tenth day, with his wound healed.

In this case the development of serious complications was prevented by prompt use of penicillin

**Case 14—D B (Fig 19)** *Diagnosis.* Orbital cellulitis—bacteriemia due to non-hemolytic streptococcus

On March 23, 1943, the Army Station Hospital in Atlantic City admitted an 18-year-old Air Force cadet who had developed severe pansinusitis following measles, and

*D B - ♂ - age 18*  
*Cellulitis left orbital soft tissue*  
*Gamma Hem strep bacteremia*

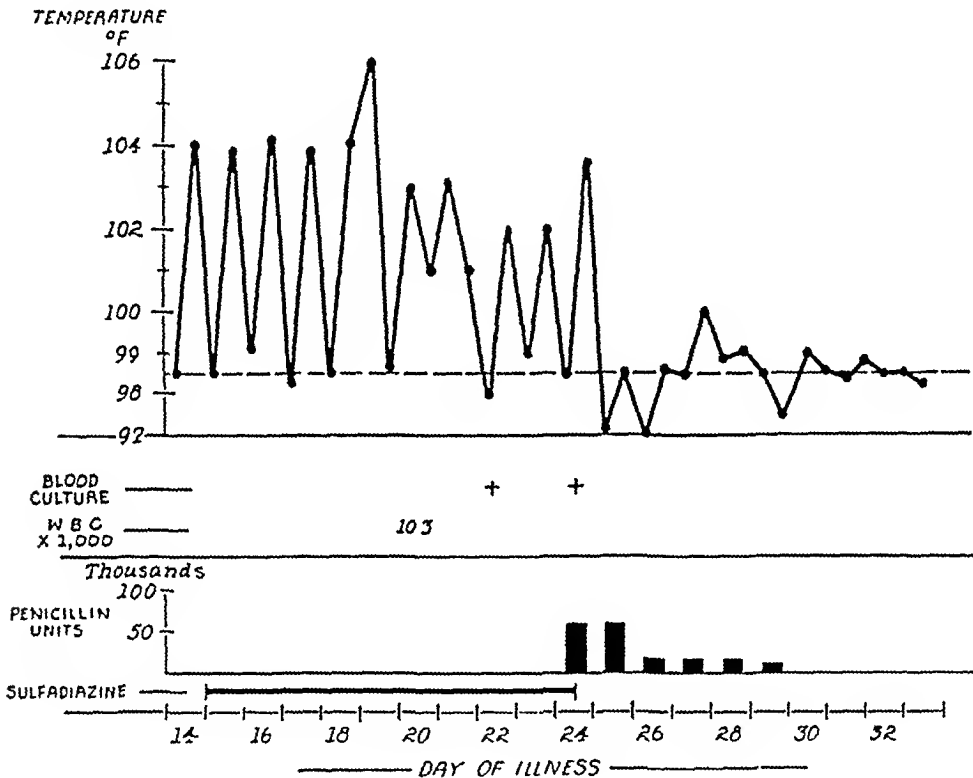


Fig 19

had been placed on sulfadiazine therapy. When a "picket-fence" temperature curve developed, two blood cultures revealed nonhemolytic streptococcus bacteriemia, and he began to show signs of orbital cellulitis, with proptosis and chemosis of his right eye. On April 10, 1943, penicillin was commenced in doses of 120,000 units per day. Rapid improvement followed, the temperature falling from 103° F to normal within 12 hours, and it remained normal thereafter. Subsequent blood cultures were negative. After three days of treatment a retro-orbital abscess pointed beneath the lateral end of the supra-orbital ridge, and was incised. Culture showed nonhemolytic streptococcus. A small amount of dilute penicillin was instilled into the cavity. Within a few days the lesion had healed completely. There was no residual evidence of damage to orbital structures. (This case is reported through the courtesy of Captain Victor R. Alfaro, M.C., A.U.S.)

**B. Boils and Carbuncles.** We have treated few cases in this category because of the likelihood of spontaneous recovery and the shortage of the penicillin supply. However, there is every reason to believe that the manage-

ment of these cases will be improved through combining penicillin therapy with surgical removal of devitalized skin, fat and fascia. Checking of the spread of cellulitis and localization of the suppurative focus usually occurs within two or three days of commencing systemic therapy. After drainage is obtained the local irrigation of the wound with penicillin solutions containing 100 to 250 units per cc seems to shorten the time of healing, but controlled observations of this effect are not yet forthcoming.

*C Pulmonary Suppuration.* We have been especially interested in the possible usefulness of penicillin in the treatment of patients with pulmonary suppuration, and in the preoperative preparation of such cases as a means of reducing the incidence of postoperative pneumonia and empyema following lobectomy or pneumonectomy. The treatment of patients with chronic putrid lung abscesses has not yielded striking results, perhaps because many of the bacteria in these lesions are resistant to penicillin. The most that can be reasonably expected of the drug in these cases is to place the patients in better condition for operation and to reduce the incidence of postoperative infection of the pleural cavity.

#### Case 15—G C (Fig 20) *Diagnosis* Chronic pulmonary suppuration

A 70-year-old white male was admitted to the service of Dr Charles Bailey, at Hahnemann Hospital, Philadelphia, October 26, 1943, for treatment of chronic pul-

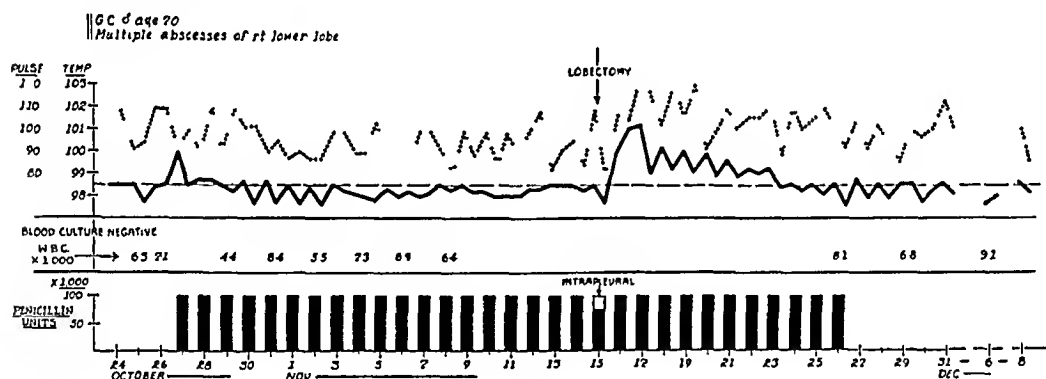


Fig 20

monary suppuration. His history was exceedingly complex, but the best clinical interpretation of his course was as follows. Perforation of a peptic ulcer in January, 1943, followed by a subphrenic abscess which ruptured first into the right pleural cavity, and then extended to involve the parenchyma of the right lower lobe. This drained spontaneously through the bronchus, but, in August, 1943, supplementary drainage was provided by thoracotomy. At the time of admission to Hahnemann Hospital he was chronically debilitated, and was raising two ounces of sputum a day, containing staphylococci, pneumococci and other mouth flora. His thoracotomy wound was still draining profusely. Penicillin was started on October 22, 1943, with 100,000 units per day intramuscularly, in preparation for lobectomy, which Doctor Bailey performed November 15, 1943. Right lower and middle lobes were removed and heavy contamination of the pleural space occurred from opening a mediastinal abscess and a collection of pus between diaphragm and lower lobe, and from division of the posterior sinus tract. The wound was closed except for a catheter drain, 25,000 units of penicillin was placed

in the cavity, and penicillin was continued by intravenous drip, and later intramuscularly, for two weeks. The patient was discharged December 8, 1943.

It is not our belief that prophylactic penicillin will eliminate the problem of empyema following contaminated lung resections. However, cases of this type offer encouragement to proceed with a careful estimation of the place of penicillin used in this way. A controlled study which is now in progress to evaluate this procedure has shown a much higher incidence of postoperative empyema in controls than in patients given penicillin before and after operation. This study will be reported at a later date.

When the lung abscess is due to infection with *Staphylococcus aureus* in pure culture it appears that penicillin will at times aid in bringing about a cure without the need for resort to surgery.

Case 16—T S (Figs 21, 22, 23, 24 and 25) *Diagnosis* Acute lung abscess, *Staphylococcus aureus*

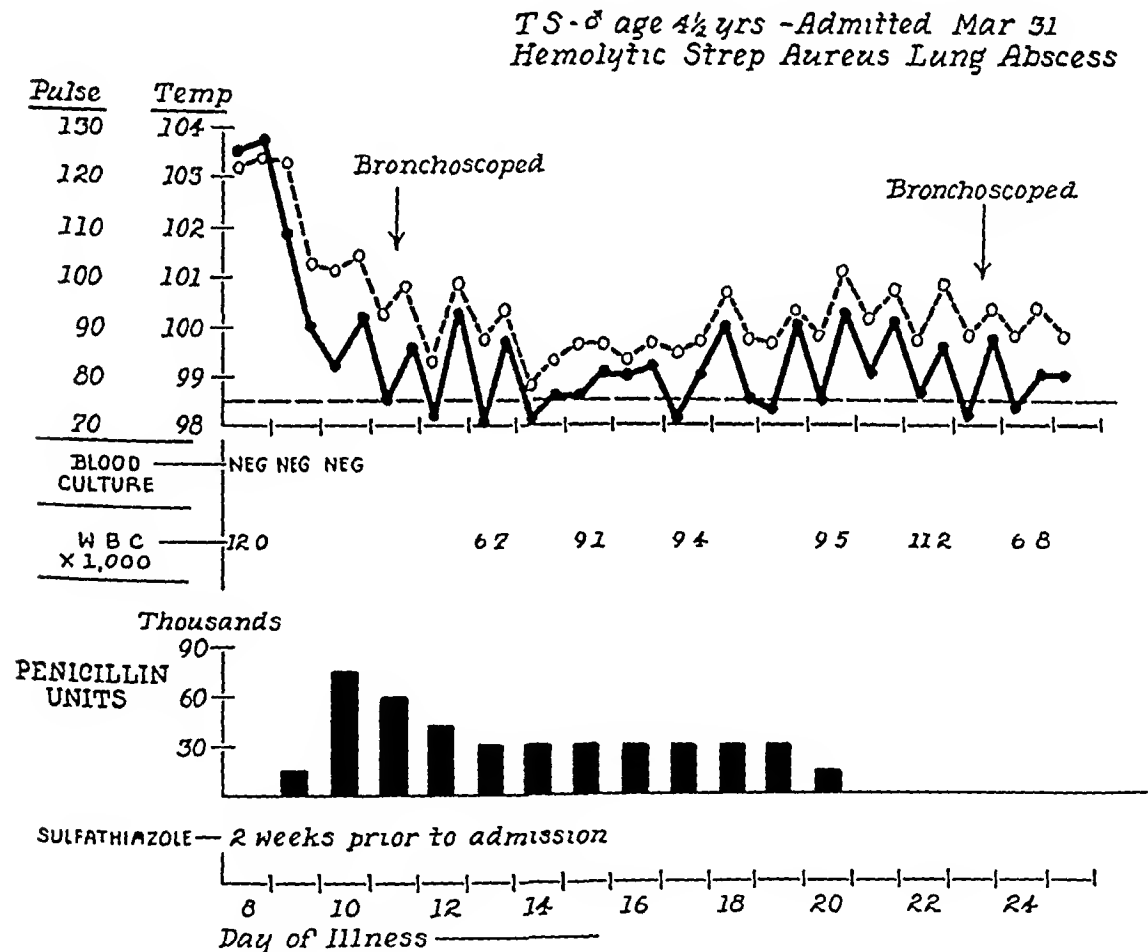


Fig 21

A four and one-half-year-old boy developed severe cough and pain in the chest following measles, and was admitted to the Children's Hospital March 23, 1943. Roentgenograms, March 27, showed a large abscess of the left upper lobe with fluid level. Bronchoscopic aspiration on March 29 yielded pure culture of *Staphylococcus aureus*. Despite sulfonamide therapy, the patient's condition deteriorated and the



FIG 22—T S Hemolytic Strep aureus—lung abscess x ray of chest day before penicillin treatment was started



FIG 23—X ray of chest four days after penicillin treatment was started



FIG 24—T S Hemolytic Strep aureus—lung abscess x ray of chest 7 days after penicillin treatment was started

abscess enlarged On April 2, 1943, penicillin treatment was commenced A second bronchoscopic aspiration was performed the following day Fever rapidly abated, and subsequent roentgenograms showed progressive disappearance of the abscess He received a total of 415,000 units



FIG 25 —T S Hemolytic Strep aureus—lung abscess X ray of chest 5 days after penicillin treatment was started

Penicillin cannot be expected to have a lasting curative effect in chronic bronchiectasis, but it may be used as a means of preparing septic cases for surgical treatment, though the striking effect brought out in the following case cannot be expected as a general rule

Case 17—B F (Fig 26) *Diagnosis* Chronic bronchiectasis

This 16-year-old girl was admitted to the Hospital of the University of Pennsylvania under the care of Doctor Simon Leopold, July 29, 1943 She had rather extensive bronchiectasis, with symptoms extending back for ten years The disease was largely

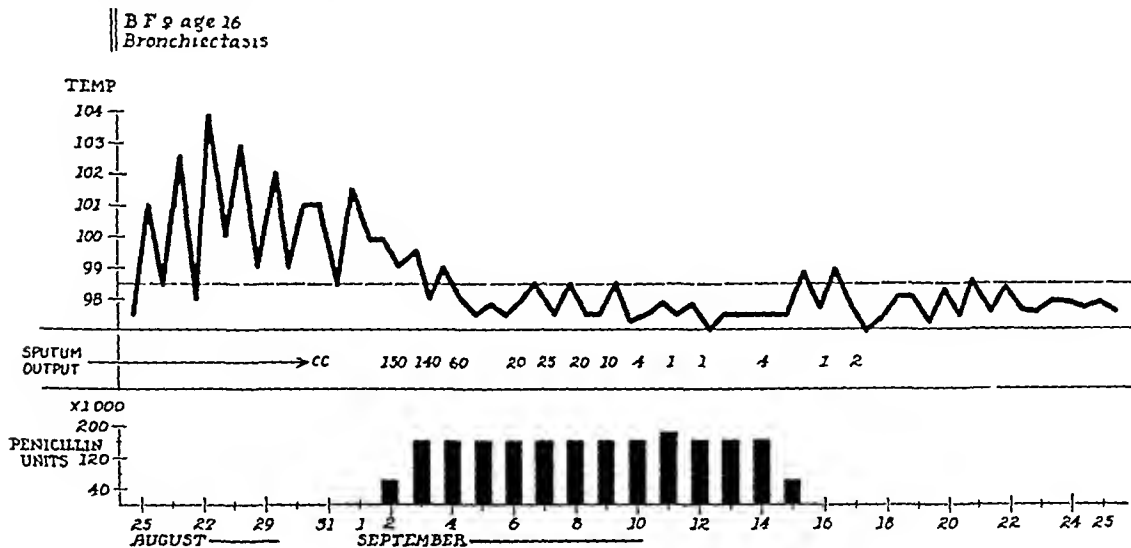


Fig. 26

confined to the left lung, and the only contraindication to proceeding with lobectomy was the presence of active pulmonary infection At the time of admission she had been running a spiking temperature for several months and was raising up to 200 cc of sputum per day Hemoglobin was 50 per cent, red blood count was 2,700,000, white

blood count was 18,000, and serum protein 6.2 Gm per 100 cc. From August 2 to August 15 she received 120,000 units of penicillin daily. Her temperature immediately dropped to normal and her appetite and sense of well-being became greatly improved. The volume of sputum decreased abruptly and by August 15 was less than 1 cc per day. Though no transfusions were given to her during this period, her hemoglobin rose to 79 per cent and the red blood count to 4,000,000. Unfortunately, she then developed a rather severe urticarial reaction to penicillin which necessitated termination of the treatment. Two weeks later Doctor Eliason was able to proceed with the first stage of a left lower lobectomy. During this interval there was no return of active lung infection. Her postoperative course, including the second stage, October 11, 1943, was uneventful, and attended by minimal febrile reaction to the surgical procedures.

This case is probably unusual in the degree of response to preoperative penicillin treatment. However, it illustrates how the drug may, in selected cases, not only control active parenchymal infection but also permit rapid

EH ♂ age 12 - admitted Mar 12  
Acute Hematogenous Osteo - Left humerus

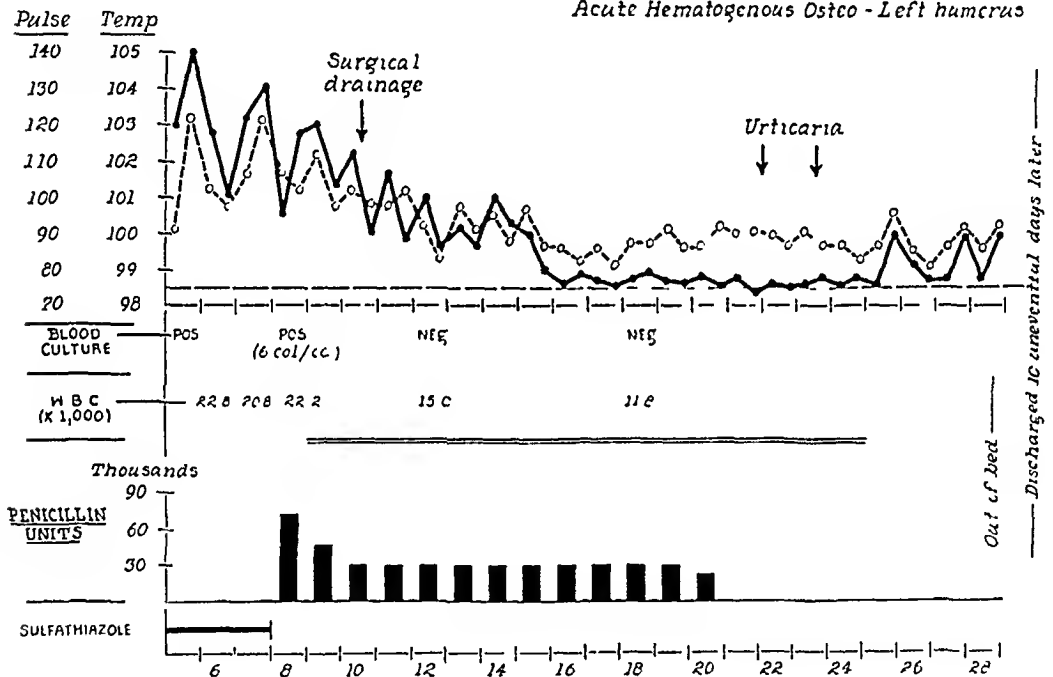


Fig 27

regeneration of blood and protein, and thereby improve the condition of the patient for a major operation.

#### LOCALIZED INFECTIONS IN BONE

**A Acute Bone Lesions** In cases of acute hematogenous osteomyelitis of long bones with or without bacteremia, penicillin therapy will usually bring about rapid disappearance of evidences of disseminated sepsis, and there usually occurs a fairly prompt regression of the signs and symptoms of local inflammation at the site of localization. The development of roentgenologic evidence of bone destruction (if not apparent at initiation of treatment) will frequently be delayed. However, in spite of continuation of treatment for



FIG 28

FIG 28—E H Acute hematogenous osteomyelitis, Staph aureus bacteremia X-ray of femur day penicillin was stopped

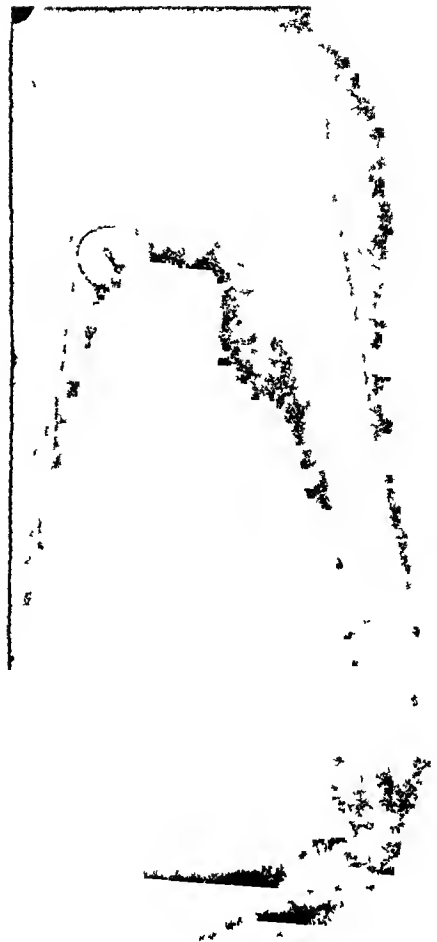


FIG 29

FIG 29—E H Acute hematogenous osteomyelitis, Staph aureus bacteremia X ray of femur 10 days after last dose of penicillin



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FIG 30—E H Acute hematogenous osteomyelitis, Staph aureus bacteremia Follow up x ray of femur 5 months after treatment



three to five weeks our cases have usually developed bone sequestra and have required surgical treatment to complete their recovery. Much more experience than is now available will be required to work out the new indications for surgical treatment of these cases. Penicillin treatment can undoubtedly be used to extend the applicability of the principle of withholding surgical intervention until a definite sequestrum has formed. Nothing has occurred in our experience to justify the hope that sequestra will become sterilized and reabsorbed, but simple areas of rarefaction in bone may occasionally become recalcified without drainage. Limitations in the supply of penicillin have prevented our treating these cases for several weeks after subsidence of the acute process, and this must be tried before final conclusions are reached.

**Case 18—E H** (Figs 27, 28, 29 and 30) *Diagnosis* Acute hematogenous osteomyelitis, *Staphylococcus aureus* bacteremia

A 12-year-old white male, patient of Doctor B F Buzby, on March 17, 1943, entered Cooper Hospital, Camden, N J, desperately ill with acute hematogenous osteomyelitis of the left humerus. Blood culture showed innumerable colonies of hemolytic *Staphylococcus aureus*. After three days of ineffective treatment with sulfathiazole when all observers had despaired of the boy's recovery, penicillin was commenced at a dose of 80,000 units per day. Drainage of an abscess of the arm was performed two days later, but the bone was not touched. He improved progressively from the time the drug was started, blood culture became negative, and within a week his temperature became normal. The drainage wound failed to heal and six months later it was necessary for him to return for sequestrectomy.

This case brings out a fact which has been strongly impressed on us, that penicillin will quite regularly control the invasive features of acute osteomyelitis but will rarely, if ever, permit permanent avoidance of surgical intervention. Frequently this may be postponed, however, until a time of election. It remains to be determined whether the extent of the eventual sequestration could be minimized by early decompression of the medullary cavity of the bone.

**Case 19—T McE** (Fig 31) *Diagnosis* Acute hematogenous osteomyelitis, *Staphylococcus aureus* bacteremia

This seven-year-old boy was first admitted to the Orthopedic Service of the Hospital of the University of Pennsylvania, August 5, 1943, with swelling and pain in the right lower thigh. Temperature was 106° F, white blood count was 21,000, and the blood culture showed 147 colonies of hemolytic *Staphylococcus aureus* per cc. After 24 hours of sulfadiazine, when the blood culture was still positive, penicillin by continuous intravenous infusion was commenced in doses of 75,000 units per day. Signs developed of bronchopneumonia and fluid in the chest, and liver and spleen became quite enlarged. However, on the seventh day of treatment he was much improved. Roentgenograms were completely negative until August 16 when slight density of the periosteum at the midfemur appeared. This did not progress. By August 24 the leg tenderness had disappeared and the temperature remained normal thereafter. He was discharged, September 12, 1943, showing moderate palpable thickening of the left thigh. Pain in the left thigh recurred in October, 1943, and he was readmitted, at which time roentgenograms revealed areas of rarefaction and definite sequestrum formation. Low grade fever was present, and he was placed in a hip spica. Close follow-up during the ensuing



bone when necessary to gain access to involved areas. A small (No 10) soft rubber catheter is laid in the wound and partial closure of the skin and subcutaneous tissue is effected around the catheter. A few cubic centimeters of penicillin-saline solution (250 units per cc) are then instilled through the catheter every four hours for four to five days, while continuing the systemic administration of the drug in doses of 80,000 to 120,000 units per day for at least an additional ten days. The local penicillin may not be necessary but is employed as an extra precaution against allowing staphylococci to multiply on the freshly traumatized wound surface and in order to assure maximum freedom of contamination of the primary zone of inflammatory fixation. When the initial dressing is performed on the fourth or fifth day the wound appears to be perfectly clean, and healthy pink granulation tissue had begun to form. The catheter is then removed and packing loosely inserted in order to prevent premature closure of the skin over a dead space. As soon as the dead space has become filled with granulation tissue the packing is omitted and the wound surfaces are allowed to come together, and may even be encouraged to do so with flamed adhesive or sutures. By this procedure complete healing has been obtained in these cases in periods as brief as 15 days. The healing process resembles that which would be expected following excision of a simple exostosis. In some instances it might be possible to perform primary closure of the wound at the time of operation, but during the present exploratory period of penicillin study we have hesitated to take much liberty with the inevitable problem of the dead space occurring after removal of bone. It remains to be seen whether such a dead space can become filled in by organization of a sterile blood clot. It should be emphasized that we have employed the above procedure only in those cases in which the preliminary period of penicillin treatment has brought about complete, or virtually complete, disappearance of pathogenic organisms from the exudate, and where thorough débridement of the infected area has been possible. Orthodox treatment is required in those instances when organisms resistant to penicillin are present in substantial numbers after fourteen days of penicillin.

**Case 20—S F** *Diagnosis* Chronic recurrent osteomyelitis

This 22-year-old graduate student had had chronic osteomyelitis of many bones over a period of ten years. Operative procedures had always been followed by prolonged drainage and healing only after many weeks or months. At this admission he showed a medullary abscess in the lower femur at the site of a previous lesion. Sulfonamides failed to cause improvement, so penicillin was started on October 18, 1943. On October 22, we performed operative drainage and curettage of an abscess in bone, connecting with one in the soft part scar. Local penicillin treatment for five days was combined with continued systemic therapy. Marked reduction in number of staphylococci was evidenced by appearance of negative plates, though positive broth cultures continued. On the fifth day after operation the wound showed no clinical evidence of infection and was, therefore, encouraged to close by application of flamed adhesive. Plastic closure was later required because of muscle herniation, but primary healing took place. Six months follow-up shows no recurrence.

**Case 21—D C** (Figs 32, 33 and 34) *Diagnosis* Chronic osteomyelitis

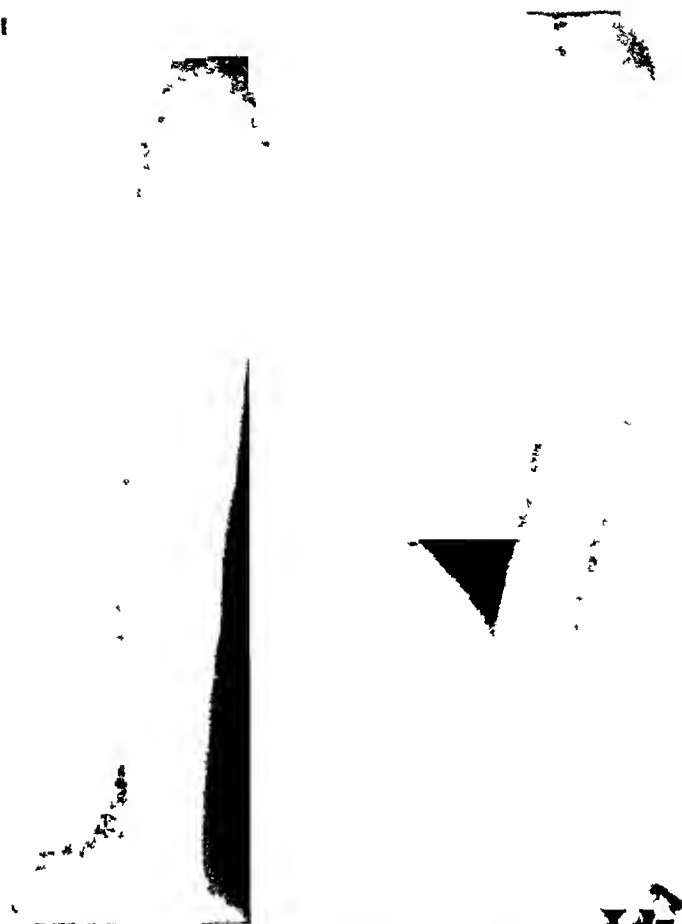


FIG 32—D C Chronic osteomyelitis X ray of femur 2½ months before penicillin treatment was started



FIG 33—D C Chronic osteomyelitis X ray of femur 4 days after penicillin treatment was started

FIG 34—D C Chronic osteomyelitis X ray of femur 2 weeks after penicillin treatment was stopped

This was a complicated case of chronic osteomyelitis of the right femur of seven years duration in a colored woman, age 28. Culture from the draining sinus on the medial aspect of her right thigh showed *Staphylococcus aureus* and diphtheroids. She was given 50,000 units of penicillin daily from January 20, 1944, to February 3, 1944, when operative debridement of two bone abscesses was performed, together with excision of chronically infected scar tissue. The areas were not saucerized. No loose sequestra were found. Cultures at the time of operation showed no growth. Deep sutures were placed, but not tied, and the wound was packed with vaselined gauze. One week later the packing was removed, sutures were tied and a circular encasement applied. Penicillin was continued intramuscularly until February 24. The encasement was removed on this day, and by February 29 the wound was completely healed. Follow-up to-date shows no recurrence of infection.

**Case 22**—M. H. *Diagnosis* Chronic osteomyelitis

This 40-year-old female had had almost continuous suppurating wounds at the sacro-iliac region for seven years and in both ilio-inguinal regions for about one year. She had had many operations at all three sites, but always the infections had recurred and, with the infection becoming entrenched in bone it had become necessary to maintain drainage continuously. On admission to the Graduate Hospital of the University of Pennsylvania, June 7, 1943, the cultures from the sinuses showed *hemolytic Staphylococcus aureus*. Roentgenograms showed involvement of the fifth lumbar vertebra, sacrum, and both ilia. Penicillin was given by continuous intravenous drip, starting out at 100,000 units per day. Within ten days of starting treatment the patient began to feel better generally, the sacro-iliac wound was healed, and the exudate from the other sinuses became thin and serous. Cultures showed marked decrease in number of bacteria. On June 25 Doctor Harry Farrell performed a superficial excision of chronically infected scar tissue overlying the lesions in the ilio-inguinal regions and removed a small sequestrum from the left anterior superior spine. Nothing was done to the major bone lesions. Penicillin was discontinued on July 3, 1943, when the patient was allowed to go home. It was expected that she would need to return for further surgery, but within three weeks both wounds became completely healed. Subsequent follow-up has shown no recurrence of infection in any of the areas. It is surprising that recurrence of infection in the fifth lumbar vertebra has not taken place.

The prognosis of these cases regarding later recurrence must remain entirely guarded. Several years of continued follow-up will be required in order to determine whether the apparently clean healing of these wounds signifies a reduced likelihood of recurrent infection in comparison with those cases in which the formation of the scar takes place in the face of prolonged suppuration. We do believe that penicillin provides an entirely new and promising approach to the treatment of these troublesome problems. In bone cases it is especially important, however, to employ careful bacteriologic control at every step of the way.

**DISCUSSION** The foregoing review of experience with penicillin offers ample evidence of the fact that this drug does give promise of meeting the previously defined limitations of sulfonamide treatment of surgical infections. In this communication we have deliberately given emphasis to the favorable results that have been obtained with penicillin in selected types of cases, and we do not wish to convey the impression that results are likely to be uniformly as good as in many of the illustrative cases presented. Penicillin does appear to have a consistently favorable influence in cases in which the organism is susceptible, and in which the anatomic and pathologic characteristics of the

lesion are such as to permit the effective transport of the drug to the site of the infection, estimation of the possibilities and limitations of penicillin therapy in every individual case should be gauged in relation to this principle. In the more resistant lesions the effectiveness of the treatment can be enhanced by increasing dosage and by making full use of surgical procedures to eradicate resistant foci, in the expectation that the drug will prevent persistence of infection in tissues of normal architecture. The scope of antibiotic treatment will be extended if current research with new substances succeeds in producing a drug which will be effective against the gram-negative bacilli which now constitute the largest group of bacteria against which no highly specific agents have been developed. Fortunately, however, these gram-negative bacilli usually depend upon symbiosis with gram-positive organisms in maintaining a parasitic state in the body, and when the pyogenic species are eliminated with penicillin the resistant types prove to possess little pathogenicity.

#### SUMMARY AND CONCLUSIONS

1 Clinical studies on penicillin in surgical infections have been conducted during the past two years under the research program of the Committee on Chemotherapeutics and other Agents and the Subcommittee on Surgical Infections of the National Research Council. Authorization has been granted to issue a general statement of tentative conclusions which may be drawn from the authors' series of 440 cases.

2 Penicillin, when administered systemically, modified the course of most infections in which the causative organism is sensitive to penicillin *in vitro*. The magnitude of the effect in individual cases may be roughly classified as follows:

a Dramatic curative responses in disseminated sepsis, particularly where circulation in localized distributing foci is adequate to effect contact between drug and bacteria. In such cases surgical treatment which would have seemed unavoidable in the past may, with penicillin, be postponed or avoided altogether.

b Favorable responses characterized by subsidence of toxemia, correction of anemia, rapid healing of infected or seriously contaminated wounds, and elimination of infection within pleural cavity or joints.

c Failures—particularly where the organism is insensitive, or where the lesion under treatment is attributable only in part (or not at all) to the persistent activity of penicillin-sensitive bacteria, and under conditions where penicillin cannot be brought to the infected area because of poor circulation or limited transport of the drug.

3 Local penicillin therapy needs further study, but is yielding encouraging results in special cases.

4 Just as with the sulfonamides, the use of penicillin requires a thorough redefinition of the indications for, and objectives in, the employment of surgery in treatment of localized infections.

5 Careful bacteriologic studies are essential if penicillin is to be used with maximal effectiveness

6 As the supply of penicillin increases it will be possible through careful observation of cases, and the use of controls whenever practical, to reach a more accurate definition of the scope and limitations of penicillin than is yet possible

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DISCUSSION—DR FRANK L MELENEY, New York Penicillin has been allotted to the units studying surgical infections under government OSRD contracts for two purposes, one, prophylactic—the prevention of infection in civilian contaminated wounds and burns, similar to the study of the sulfonamides which has been going on during the past two years, and the other, the active treatment of established surgical infections

It will take some time to gather and analyze the data on prophylaxis with penicillin. It has only been available for the last six months for the study of compound fractures of the long bones of the lower extremity in four units, and the numbers are not yet sufficient to permit drawing conclusions

Penicillin has been available somewhat longer in these Units for appraisal in established surgical infections, and more of these cases have been available. Doctor Lockwood's Unit has had the broadest experience of any of the Units, having treated 440 established infections with penicillin, and at least half of these cases have been surgical infections. This is the largest group of surgical infections in civilians that have been reviewed. We had, of course, Doctor Lyon's fine paper reporting the results of his treatment of returned soldiers, mostly with infected compound fractures, all of whom, I would like to point out to Doctor Key, had had sulfonamides

Let me reiterate the fact that the appraisal of drugs is more difficult in surgical infections than in medical infections, because surgical infections are characterized by a local breakdown of tissue or a confined localized exudate which must be evacuated either spontaneously or by a surgical procedure, or must be absorbed by the body

These necrotic exudative foci may prevent the entrance of the therapeutic agent or nullify its action when it gets to the focus. Furthermore, the rapidity of recovery from such infection depends greatly upon the time relationships between the onset of the infection, the administration of the drug, and the surgical procedure.

The problem of the appraisal of drugs in surgical infections is, therefore, much more complicated than in medical infections.

Drug therapy may be said to be effective in surgical infections, either (1) if it obviates the surgical procedure entirely, (2) if it permits a more limited type of surgical procedure than would otherwise be necessary, (3) if it permits primary closure immediately after removal of the dead tissue or exudate, (4) if it permits earlier secondary closure than usual, and (5) if it shortens the time of the control of the infection.

The first and third of these five criteria are fairly clear-cut, namely, obviating surgery and permitting immediate primary closure. The other three are comparative, and drug-treated cases must be compared with adequate controls.

Surgical infections also permit the local as well as the general administration of drugs, and this offers three methods to be appraised—local, general and both combined—with the necessity of considering the local and general toxic effects as well as the therapeutic effects of the drug.

As Doctor Lockwood has pointed out, both the sulfonamides and penicillin have brought out the importance of determining the exact bacterial etiology of the infection under consideration. Neither of them should be used indiscriminately. Penicillin has the very great advantage over the sulfonamides in that (1) its toxic limit (and I do not know whether that has ever been determined for man) is far above its therapeutic level, (2) it is not inhibited by blood or pus or necrotic tissue, and (3) when used locally it minimizes and does not increase exudate.

Penicillin has the disadvantage, however, of being inactivated or inhibited by many of the gram-negative bacilli, and of not working well when there are mixtures of organisms. In fact, its outstanding performance in surgical infections has been in those cases in which the causative organism has been the *hemolytic Staphylococcus aureus*, where the sulfonamides have fallen down so badly.

The unit at the Presbyterian Hospital has been able to study about 150 established surgical infections treated with penicillin, and about one-third of these were treated locally only.

In this respect our experience has differed considerably from Doctor Lockwood's, and in this field I think there is a possibility of wide usefulness of this drug with a minimum expenditure of material. Results have been obtained by local use alone, which I believe fulfill some of the criteria of effectiveness mentioned above.

I would like to show three slides to illustrate the value of local penicillin and two others to illustrate other points.

Chart I is a case of a very large abscess of the axilla due to an hemolytic streptococcus. On the second day it was aspirated without much change, although 400 cc of pus was removed. On the 4th day a small incision was made at the bottom of the abscess, allowing the exudate to come out, and, through a tube, penicillin was introduced every three hours in 5,000 unit quantity. The immediate response was remarkable.

This is the combination of a minor surgical procedure with the local use of penicillin, 40,000 units were used each day, and it was stopped after six days. I believe, now, that we might have used very much less penicillin locally than we did, and could have given it less frequently.

Chart II is a case referred by Dr. William White, of our Association—that of a girl who had had two large abscesses of the face which had been operated upon, leaving scars. She had a third large abscess of the cheek which bulged into the mouth, and when he sent her to me he said, "If possible make your incision within the mouth rather than on the outside, to avoid another visible scar."



There was a tiny opening, however, on the outside through which, with a blunt needle, penicillin could be introduced. This was instilled daily, with from 2,500 to 3,500 units a day. There was prompt subsidence of the inflammation, and no incision was necessary at all.

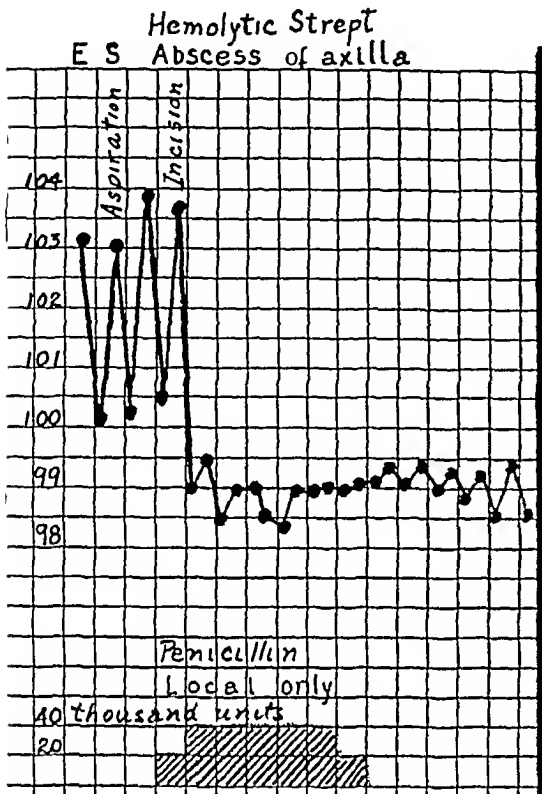


CHART I

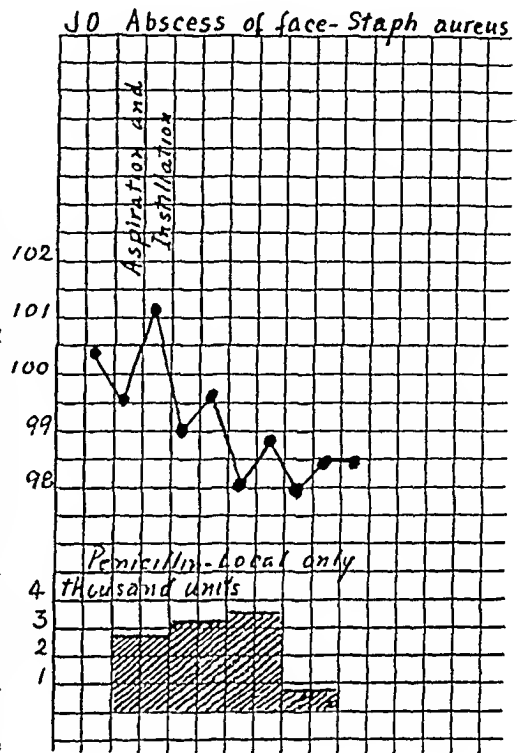


CHART II

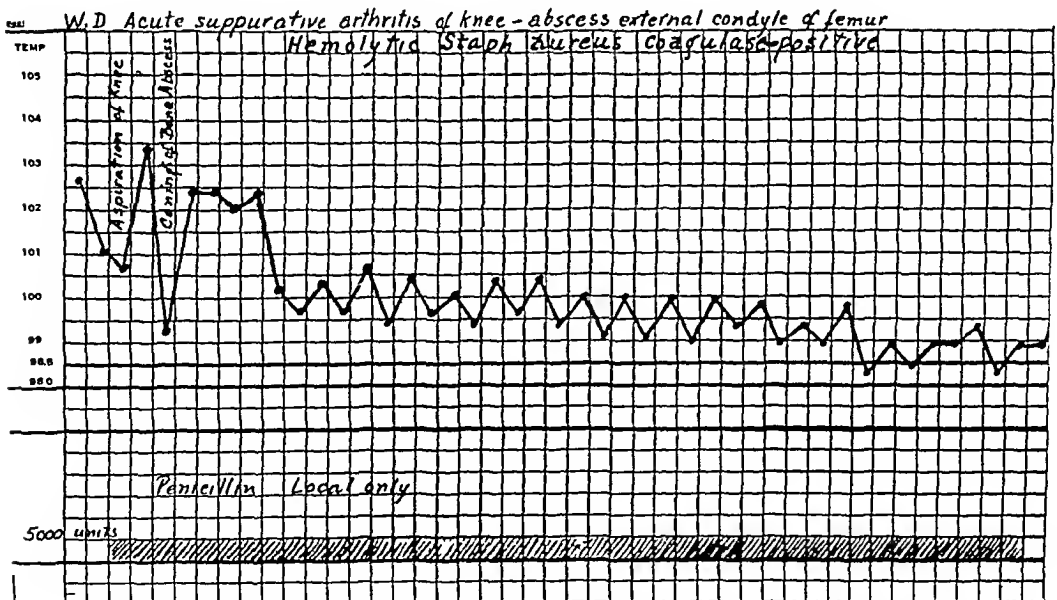


CHART III

Chart III is a case who had an acute abscess in the external condyle of the femur with an acute suppurative arthritis of the knee. When this patient was admitted, the knee was aspirated, and 5,000 units of penicillin were introduced. I planned the next day to open the knee joint as well as drain the abscess in the bone, but the knee showed no reaccumulation of fluid, so the bone cavity was unroofed and a China silk tampon was placed within the cavity, with 5,000 units of penicillin on gauze packing within the silk

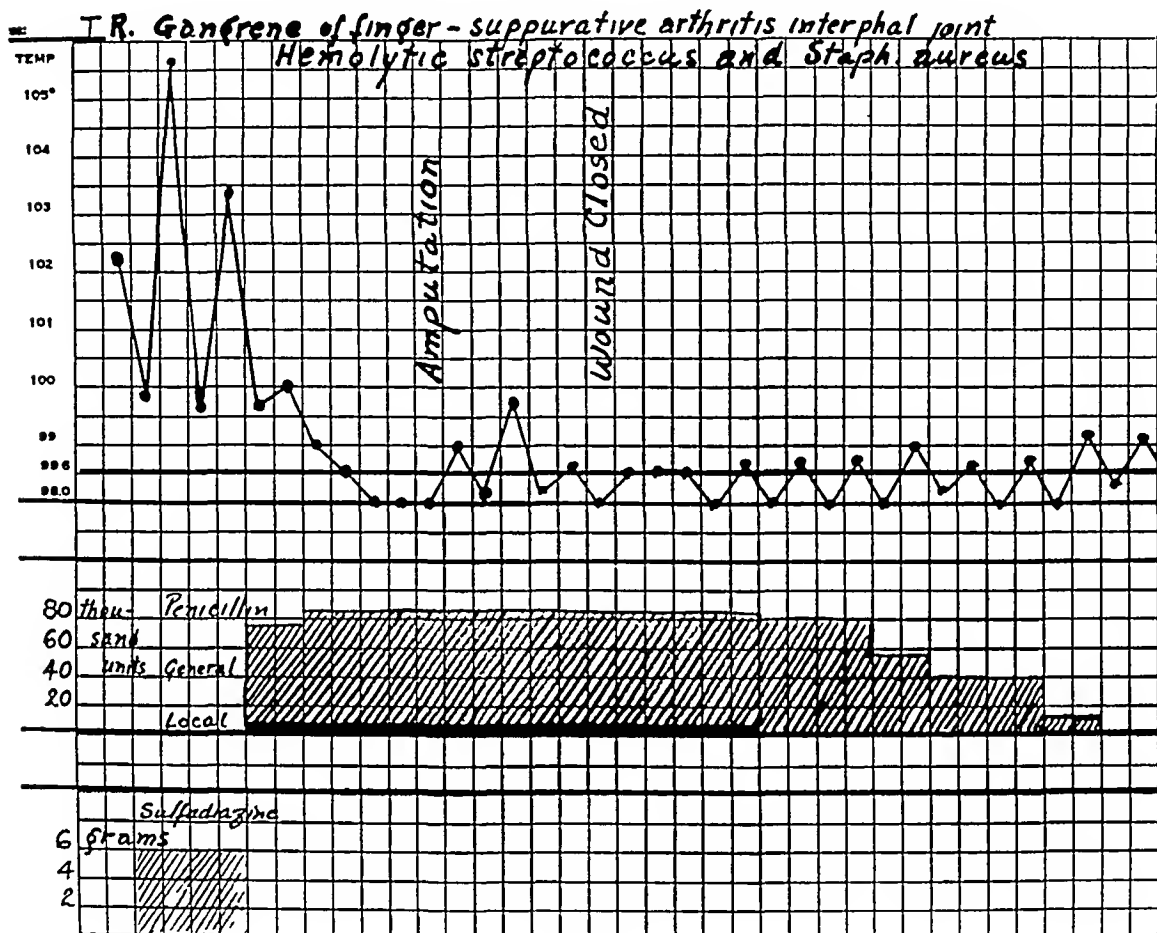


CHART IV

tampon. The packing was replaced daily, and the response was gratifying. When the silk tampon was removed on the ninth day, the bone cavity was lined with granulations. He was out of the hospital on the 26th day. The wound was all healed in less than six weeks, and he had perfect function of his knee joint, which received only one instillation of penicillin, and was not opened.

Chart IV illustrates a late primary closure. The patient was a young merchant-marine cadet, with an acute suppurative arthritis of the first interphalangeal joint of the left index finger. The infection, with both *hemolytic Staphylococcus aureus* and *hemolytic Streptococcus*, had dissolved the extension tendon and the joint surfaces. Amputation was performed through the joint, with a long anterior flap, which was left open. He received both local and general penicillin. The exudate ceased, the streptococci disappeared from the wound, and the staphylococci were greatly diminished in numbers. The wound was closed on the third day, and healed without any evidence of infection, penicillin being continued locally by instilling between the stitches once daily for three days and general penicillin being continued for five days more.

Chart V illustrates two cases of gas gangrene. The curve on the left shows a case of acute gaseous gangrene of the abdominal wall which followed drainage of the common

duct after removal of a common duct stone. The wound was opened up and the necrotic muscle removed and local zinc peroxide was applied—50,000 units of penicillin were given intravenously every three hours. Antigas gangrene serum in large doses was given. The temperature fell next morning, but she developed jaundice and suddenly died.

On the right of the chart is shown the temperature curve of the patient with a *Clostridium sordellii* infection. It is very rare of course. The jelly-like edema spread rapidly, in spite of wide incisions, and 50,000 units of penicillin every three hours. In this case there was no evidence of any effect, the temperature rising steadily until death.

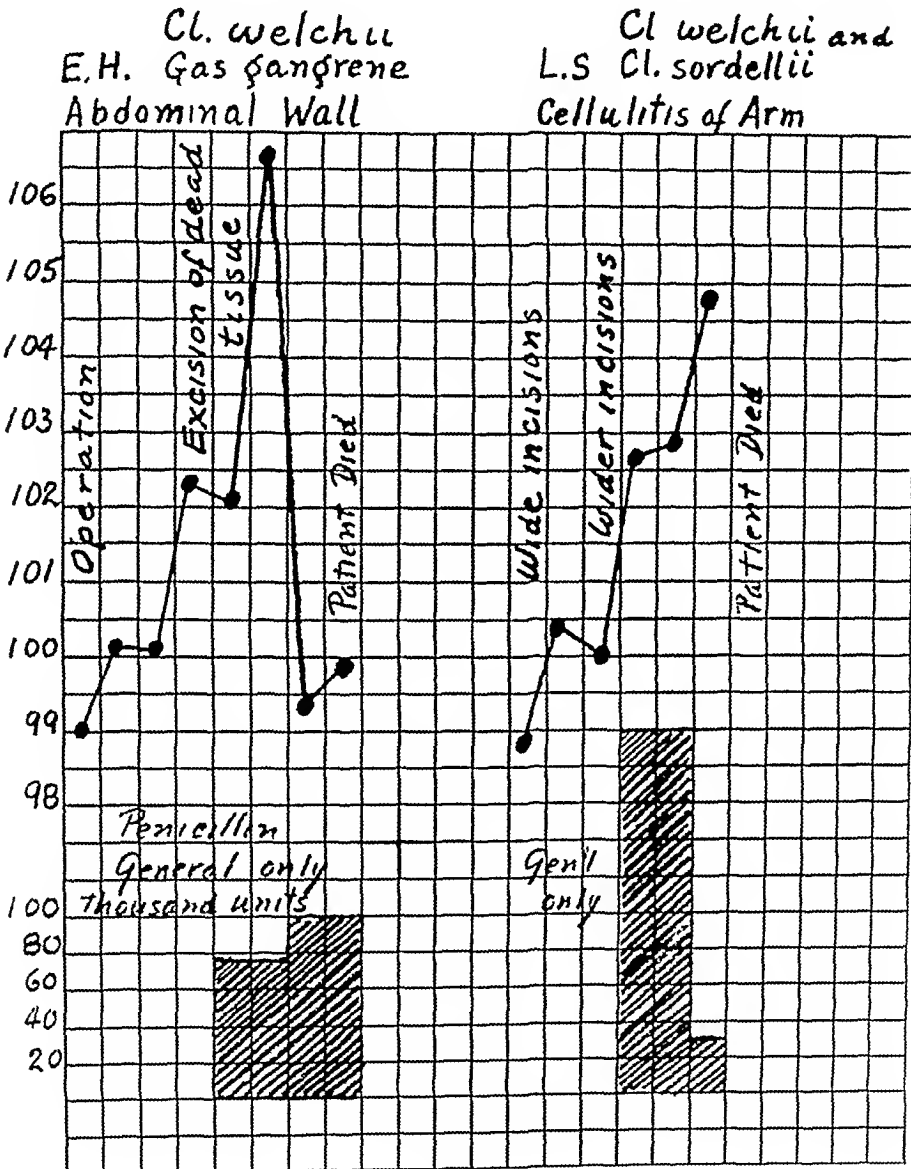


CHART V

In conclusion, I would like to simply say that the evidence seems to be slowly mounting that penicillin is going to meet the great need of preventing the general spread of infection from a local process due to the hemolytic *Staphylococcus aureus*, just as the sulfonamides have prevented the generalized spread of infections due to the hemolytic *Streptococcus*. Where the process is well localized, the local use of penicillin frequently hastens the control of infection, and may obviate a surgical procedure.

Penicillin has not satisfactorily met the problem of gas gangrene, and this may be due not only to the greater resistance of the causative organisms but to the fact that gas gangrene is a polymicrobial disease with gram-negative organisms frequently present, which frequently inhibit the action of penicillin. This is also true of other war wounds, and time alone will tell whether it is going to be effective in cutting down the incidence of local infection in damaged tissues.

One report, received very recently, indicates that it has not done so thus far. The immediate need is apparent for intensive work to be done to find something that will knockout these penicillin inhibitors—the gram-negative bacilli. Whether that will be in the field of chemotherapy or antibiotics, time alone will tell.

# ACUTE STARVATION FOLLOWING OPERATION OR INJURY. WITH SPECIAL REFERENCE TO CALORIC AND PROTEIN NEEDS\*

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IN HIS CLASSIC TEXT,<sup>14</sup> Lusk defines starvation as the "deprivation of an organism of any or all of the elements necessary to its nutrition" These nutritional elements, six in number, *i e*, water, salt, protein, fat, carbohydrate and vitamins, must each be considered in discussing starvation not only to achieve completeness, but because they are biochemically interdependent For example, certain of the vitamins are now known to be necessary for the metabolism of carbohydrate Carbohydrate, moreover, seems to be necessary for the proper utilization of protein Of most significance is the fact that water and electrolyte balance is greatly disturbed by protein deficiencies due, in part at least, to a lowering in the concentration of plasma protein

In actual surgical practice measures nearly always are taken to prevent water and electrolyte starvation, this is not particularly difficult, even when patients are unable to take anything by mouth, by the simple injection of physiologic saline solution In addition, most patients receive a certain amount of carbohydrate sufficient at least to prevent ketosis, though usually insufficient to meet all of the caloric needs Vitamins, neglected for a great many years, now are given adequately even if the patient is unable to take any by mouth The remaining elements are fat and protein For the present discussion, fat and carbohydrate will be considered under the one heading of caloric or energy requirements This, strictly, is not justified over long periods, inasmuch as fat contains food essentials entirely apart from its calorogenic function However, during short periods these considerations may be overlooked and caloric requirements, therefore, will be considered as one food essential regardless of whether it originates from fat or carbohydrate Thus, acute starvation in most surgical patients probably is confined to protein and caloric (energy) needs, and most of the present discussion will be devoted to them

Deprivation of protein and caloric needs wholly or partially, although frequent, is, in general, viewed with complacency or considered inevitable The supposition that tissue and other stores will supply safely the needs of the body has lulled us into a false security, as a result many surgeons are not aware of the deleterious results produced by such starvation, even though manifestations may be subclinical Wastage of body tissue, particularly tissue and plasma protein, is not without untoward effects which begin

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almost at once after protein is removed from the diet. Thus, it becomes important to study the causes and the effects as well as the means for the prevention and cure of starvation. Such study will undoubtedly lead to a more rapid and uncomplicated convalescence and raise surgical therapy to a higher plane of efficiency.

#### CAUSES OF STARVATION AFTER INJURY OR OPERATION

Only patients well-nourished at the time of injury or operation will be considered herein. For the sake of brevity, cases will be eliminated in which starvation is due to economic or other causes or to diseases themselves responsible for malnutrition.

When a healthy, well-nourished individual sustains a serious injury or undergoes a severe operation, starvation nearly always ensues. While the causes of such starvation are those which lead to deprivation of one or more of the nutritional elements, there is another factor which increases the need for one of them. As a result of injury, as shown so well by Cuthbertson,<sup>6</sup> there follows an unusually large breakdown of protein tissue, usually called "toxic destruction of protein," which leads to protein depletion even with the intake of a normal well-balanced diet. Although it is probable that an unusually large protein intake may prevent such loss of protein tissue, further study of the nature of this phenomenon is needed. Similar in its effect is the abnormal loss of protein in discharges or exudates of one type or another, as in peritonitis, empyema, burns, damaged tissue, or from large open wounds.

Even though the food requirements are normal and the patient is able to eat, the dietary intake after injury or operation is nearly always inadequate, due to several causes. Starvation is often imposed by the surgeon in charge because he fears that the ingestion of food will prove deleterious. Sometimes the patient himself is apprehensive. Often only fruit juices and broth are permitted, such an intake leads to electrolyte or protein starvation or both. Excluding cases in which it is necessary to keep the gastro-intestinal tract at rest as in general peritonitis, or in which vomiting is present, such fear is usually without foundation. On the other hand, when the patient cannot eat or is vomiting, protein starvation will ensue because the usual parenteral injections contain only electrolyte and glucose.

Starvation in other patients, while not imposed, is due to partial or complete loss of appetite, which is a frequent manifestation after injury or operation, aggravated often by oversedation, particularly the frequent use of morphine. Thus, there follows a failure in the normal impulses which ordinarily insure an adequate intake of food, and the patient, left to his own resources, does not eat, even when perfectly adequate trays of food are served. Ordinarily, anorexia ends quickly and spontaneously and the patient soon begins to eat of his own accord, however, in many cases, anorexia persists and becomes a manifestation of starvation itself. Thus a vicious cycle is established by which the very effect of starvation becomes a further cause.

## THE EFFECTS OF ACUTE STARVATION AFTER INJURY OR OPERATION

The following manifestations are arranged in six arbitrary groups and are probably incomplete. As will be noted, most of the effects are due largely to protein starvation.

1 *Loss of weight* is of frequent, perhaps universal occurrence after severe injury or operation, even though its degree is perhaps not fully realized, and, indeed, may be partly masked in the most severe cases by retention of water. In a brief survey of our cases treated by the orthodox dietary regimen, loss of weight was universal and occasionally surprisingly great, for example, one patient suffered a decline of 25 pounds after a relatively uncomplicated cholecystectomy. Of particular interest in war surgery are the findings of Lyons,<sup>10</sup> who, in a series of compound fractures in American battle casualties, observed a loss of weight of from 5 to 30 kilograms (11 to 66 pounds).

Loss of body weight may not be a quantitative measure of the degree of starvation because changes in water content, which occupies 70 per cent of the body weight, are frequent and marked, and introduce a complicating factor. For example, nutritional edema may add many kilograms to body weight and even mask completely the wastage of body tissues. On the other hand, loss of weight in a patient with nutritional edema means absorption and excretion of the excess water, which is the first indication of *improvement* in the protein deficiency. Even in the absence of edema, increases in the extracellular fluid volume may add significantly to the body weight, as shown by Lyons,<sup>10</sup> and thus also masks the actual degree of tissue loss. Moreover, water retention and excretion may also be influenced by a change from a high fat to a high carbohydrate diet or *vice versa*, respectively, as shown many years ago by Benedict and Carpenter.<sup>1</sup>

If water balance is maintained or its influence taken into account, loss of body weight means loss of body tissue, but its physiologic significance depends upon which of the two body tissue depots is depleted, *i e*, whether the loss affects the fatty or the protein tissue. Physiologic impairment follows depletion of tissue, including plasma protein, whereas adipose tissue can be used without such impairment, indeed, in the obese, loss of fat probably increases physiologic performance. The clinical significance of loss of body weight depends, therefore, upon the degree of protein depletion involved.

Loss of protein tissue can be measured clinically by the amount of nitrogen excreted, inasmuch as all protein tissue, when broken down, results in the terminal excretion of nitrogen largely as urea and ammonia. Actual studies have indeed shown that after injury or operation as much as 20 to 40 Gm of nitrogen may be excreted per day. This ( $\times 6.25$ ) means 125 to 250 Gm of protein or in terms of protein tissue, which is 80 per cent water, 0.6 to 1.3 kilograms (1.5 to 3 pounds). From this calculation it is easy to see how surgical patients are able to show such huge losses in body weight within a short period of time. By contrast, loss of fatty tissue to supply calories is much less. Even if all of, say, 2000 calories were supplied

by fat, this would represent but 200 Gm, or in terms of the tissue itself, which is but 20 per cent water, 240 gm or one-half pound a day

2 *Mild Clinical Manifestations*—Surgeons are accustomed to attribute most of the postoperative weakness or asthenia to the operative procedure without realizing that much of it may actually be due to starvation, particularly deprivation of protein. According to Youmans<sup>24</sup> protein deficiency produces symptoms of fatigability and muscular weakness, which he states can scarcely be considered specific in the presence of deficiencies of other elements in the diet. However, in an interesting investigation by Mueller, Fickas and Cox,<sup>17</sup> normal humans ingested a diet complete in all elements except protein and found that after 48 hours severe symptoms of lassitude and asthenia developed which were corrected rapidly by the ingestion of protein food. Thorne, Quinby and Clinton<sup>22</sup> showed a similar influence of protein in an even shorter period of time by feeding a trained subject isocaloric breakfasts containing an abundance of fat, carbohydrate or protein. Only the meal with a high protein content failed to produce hypoglycemia and symptoms of hunger and lassitude after several hours. The present writer has often observed that postoperative weakness was improved by the intravenous injection of hydrolyzed protein.<sup>9, 12</sup> The most complete and convincing evidence, however, of the influence of food on postoperative asthenia is that described by Mulholland, Co Tui, *et al*,<sup>18</sup> who showed how jejunal alimentation, beginning immediately after operation, alleviated most of these symptoms and accelerated convalescence in a series of gastric resections. Many factors are undoubtedly responsible for postoperative weakness and asthenia, but the evidence mentioned certainly suggests that starvation, particularly of protein, is of great significance.

3 *Serious Clinical Manifestations*—Nutritional edema is probably one of the most important of the serious clinical manifestations of starvation and may involve the gastro-intestinal mucosa, producing severe symptoms, including those of intestinal obstruction.<sup>19</sup> Nutritional edema is probably also responsible for such phenomena as delay in wound healing, anuria and even circulatory impairment.<sup>8</sup> All of these complications have been observed after severe injury and operation, though often attributed to other causes. Although physical factors play a rôle, hypoproteinemia long has been recognized as the most significant cause of nutritional edema. A complete analysis of the important effects of starvation has been described at some length in the monograph of Jackson.<sup>13</sup>

4 *Lowered Resistance to Infection*—The influence of starvation, particularly of protein, on the immunologic response of the body, has been studied by Cannon, Chase and Wissler.<sup>4</sup> They have shown that the production of antibody is but one-third to one-fifth as great in protein-deficient animals with hypoproteinemia as compared with those on a regular diet. It is probable from these important and convincing observations that many postoperative infections may be due in part to a lowering of the immunologic response of the body, which is secondary to protein starvation.



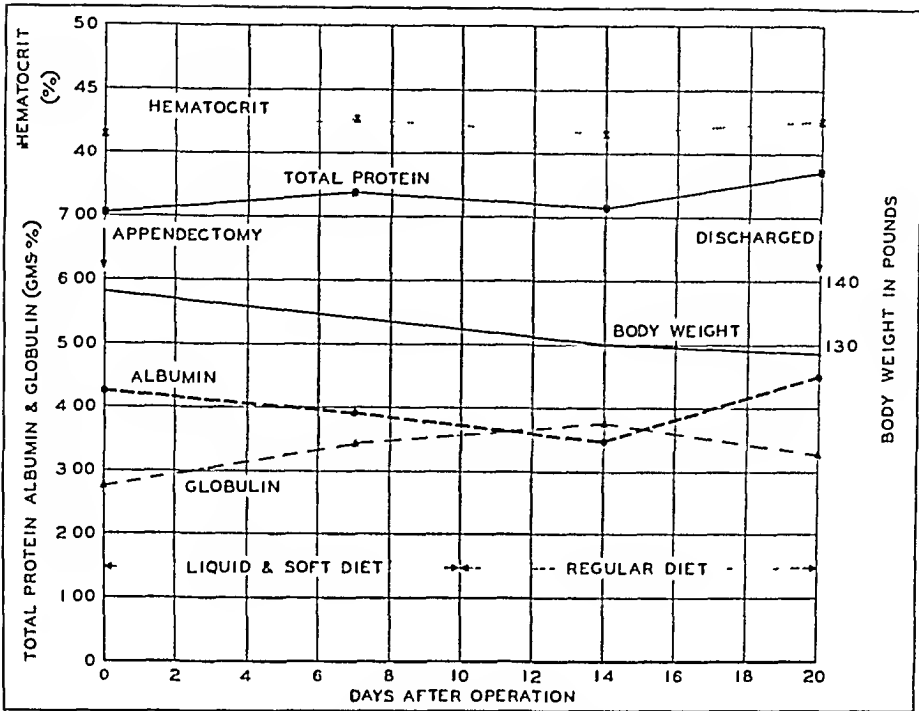


CHART 1—Hypoproteinemia masked by hyperglobulinemia in a 55 year old male following appendectomy for acute appendicitis. Note the normal total protein, the fall in the level of plasma albumin was masked by a corresponding increase in the globulin fraction which was due to a moderate wound infection. There was a loss of eight pounds in body weight. Note the return of the albumin fraction to normal on resumption of a normal diet.

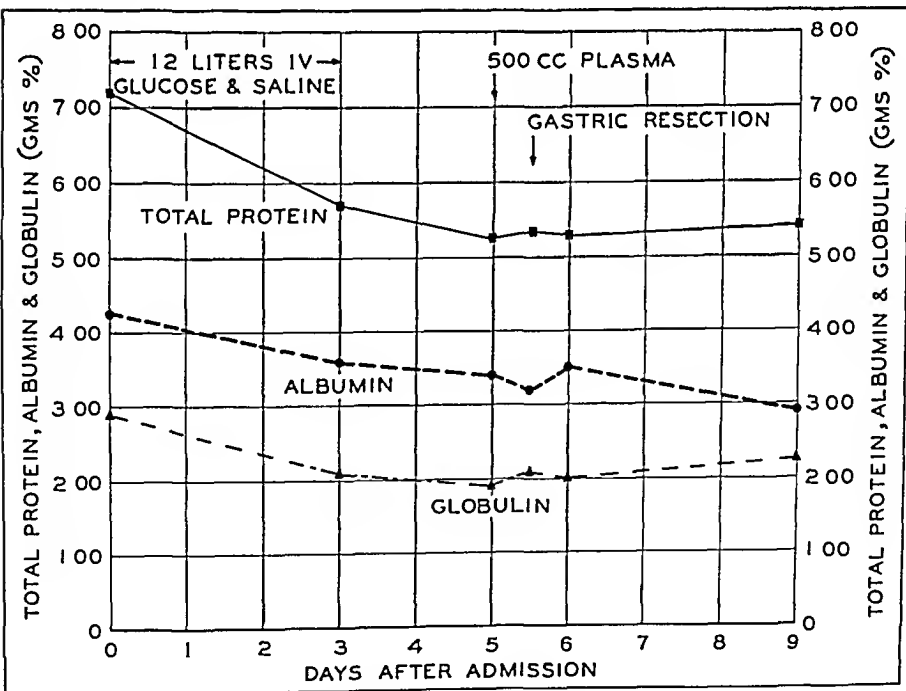


CHART 2—Hypoproteinemia masked by dehydration in a 60 year old male with pyloric obstruction due to carcinoma. Note the normal plasma protein on admission, although patient had lost 25 pounds in body weight, correction of dehydration by parenteral saline was accompanied by the appearance of hypoproteinemia which was uninfluenced by a 500 cc plasma transfusion.

5 *Hypoproteinememia*—A fall in the level of serum protein after operation or injury may be the first evidence of protein depletion, just as a fall in the vitamin C content of the blood precedes clinical signs of scurvy. Published data on the extent of hypoproteinememia after operation vary considerably, although Casten and Bodenheimer<sup>5</sup> have reported a postoperative fall in the total plasma protein concentration of 0.5 Gm per cent or more in 20 to 100 per cent of their cases. Hypoproteinememia frequently escapes detection because its existence is masked by two factors discussed in a previous paper.<sup>10</sup> One of the factors is based upon the fact that the albumin fraction is the one significantly involved in malnutrition, yet many patients with hypo-albuminemia will show a normal value for total proteins because of an increase in the globulin fraction which often is due to infection. The other factor is dehydration, which is responsible for a normal concentration of both fractions, though the total amount of circulating protein is depleted. An example of each is presented herewith in Charts 1 and 2, respectively.

That a fall in circulating plasma protein occurs very promptly on withdrawal of protein from the diet has been demonstrated experimentally. Whatever stores of protein exist for the replacement of serum protein lost by hemorrhage, burns, *etc*, they certainly do not seem to function when the protein is lost because of starvation. Thus, Weech<sup>23</sup> has shown very clearly, and his observations have been confirmed in our laboratory,<sup>11</sup> that the fall in plasma albumin begins with the very onset of a protein deficient diet. In the human, Cutting and Cutter<sup>7</sup> have confirmed these findings in a study of 26 normal individuals subjected to a 48-hour period of partial starvation. Even in this short period there was a fall of 10 per cent in the total amount of circulating plasma protein. Significantly, they showed that in spite of this loss the concentration of plasma protein was unchanged or even increased because of dehydration.

6 *Death*—That a fatal outcome after injury or operation may be due to starvation certainly would be surprising in this land of plenty. Yet this has been an inescapable conclusion in several instances, although the recorded cause of death was, of course, the disease itself, or one of its complications. In such cases, extreme emaciation is the prominent finding at postmortem, with the surgical lesions corrected or of themselves insufficient to account for death. Inasmuch as death is an inevitable result of starvation in normal individuals, it is not surprising that those suffering from some injury or disease also may die because of an inadequate intake of food.

#### TREATMENT OF STARVATION

In most cases the treatment of starvation is astonishingly simple and consists merely of methods aimed at overcoming the patient's loss of appetite. To do so, however, the surgeon in charge must view anorexia as a therapeutic challenge, not as a necessary symptom. An adequate food intake is often possible even in the presence of severe anorexia if palatability is increased and nursing care provided. Idiosyncrasies may have to be given

consideration Sedation, including morphine, should be used judiciously and bodily movement encouraged as much as possible Moreover, the diet must be complete and in particular contain adequate protein It is hard to understand the vogue of fruit juice, which contains merely carbohydrate and vitamin C, is entirely deficient in salt and protein,<sup>2</sup> and, thus, will lead inevitably to electrolyte and protein starvation when taken as the sole article of the diet Ordinary broth, likewise, is an inadequate fluid, although a good source of salt, inasmuch as it contains in most cases a very tiny amount of protein, we have analyzed several broths and found less than one gram of protein in a cup of it Milk is an excellent food and extremely valuable as a drink, although its water content is unnecessarily high A much more concentrated and convenient high protein, high carbohydrate drink can be made up very readily by stirring 100 grams of skimmed milk powder into 200 cc of water This furnishes 34 grams of protein and 52 grams of carbohydrate, which exceeds that in a quart of milk, in one-fifth its volume Three glasses of this liquid will meet the daily protein needs of a normal-sized adult Solid food, as eggs and meat, should be added as soon as possible Most postoperative patients can eat food much earlier than they are usually permitted to In other words, eating should be encouraged rather than discouraged, often a simple statement by the surgeon will go a long way in overcoming anorexia and thus preventing starvation

In spite of all that can be done with encouragement, special food and fluid, and nursing care, it is often difficult or impossible to get a patient, after operation or injury, to take a full, well balanced diet Tube feeding may be employed, but has many obvious disadvantages The actual amount of food necessary to furnish, say, 2000 calories, is fairly large and presents practical difficulties because of its bulk This is especially true when feeding must be parenteral, for example, it would be necessary to inject each day eight liters of 5 per cent glucose to produce 1600 calories, the barely minimum requirement for an average-sized adult The problem can be made easier by sacrificing some and perhaps even a considerable part of the caloric requirements This is possible without producing serious physiologic impairment because caloric deprivation involves merely the loss of tissue fat, which may be considered as a nonessential tissue and thus is a true (dispensable) store of body food

*Caloric Versus Protein Requirement*—From the theoretic point of view, body fat should be able to supply a great deal of the energy requirements in the absence of caloric intake in food Lusk<sup>15</sup> stated that under conditions of complete starvation about 87 per cent of the total energy actually is derived from tissue fat This is an important consideration, inasmuch as 80 per cent of an ordinary well balanced diet consists of food furnishing calories, whereas but 20 per cent is protein By dispensing with even part of the large proportion of the diet devoted to calories, the practical problem of postoperative nutrition becomes greatly simplified How much of it can actually be sacrificed? A small amount of carbohydrate undoubtedly is necessary to prevent

ketosis Moreover, Thomas<sup>21</sup> has shown that nitrogen balance cannot be achieved with protein alone Brunschwig, Clarke and Corbin<sup>3</sup> could not achieve nitrogen balance with intravenous injections of hydrolyzed protein alone What, actually, is the minimum amount of carbohydrate which is necessary in order to prevent ketosis and to insure adequate utilization of the ingested nitrogenous food? If this were known, starvation could be prevented with a relatively restricted diet without producing physiologic impairment The minimum requirements then would consist merely of sufficient food to maintain water, electrolyte, nitrogen and vitamin balance Caloric balance could thus be waived at the expense of tissue fat

Evidence that nitrogen can be stored when the daily caloric requirement is reduced by 33 per cent was described by Rubner<sup>20</sup> The present author for several years has injected a mixture of equal parts of glucose and hydrolyzed protein into patients intravenously and frequently observed positive nitrogen balance, even though the caloric intake was far from adequate to meet the daily needs Further observations are in process to determine just how much of the caloric intake may be safely left to body fat In the accompanying table the results of one preliminary experiment are described Two dogs were given a diet consisting of different proportions of carbo-

TABLE I  
NITROGEN (N) BALANCE WITH TWO DIFFERENT PROPORTIONS OF PROTEIN AND CARBOHYDRATE  
*Note the larger and increasing retention of nitrogen with the high protein diet (2) as compared with the more normal proportion in diet 1*

Periods	Dog 1—Diet 1 20% Protein, 80% Carbohydrate			Dog 2—Diet 2 80% Protein 20% Carbohydrate		
	N Intake	N Output	N Balance	N Intake	N Output	N Balance
I (3 days)	32	26	+ 06	1 28	1 03	+ 25
II (4 days)	32	24	+ 08	1 28	93	+ 35
III (4 days)	32	29	+ 03	1 28	70	+ 58
Average	32	26	+ 06	1 28	89	+ 39

All figures are in grams per kilogram per day The total caloric intake in each experiment was 40 per kilogram per day, this was probably inadequate because each dog was malnourished, having been on a deficient intake for the two weeks previously The protein employed was dried scales of egg albumin (Merck) the carbohydrate Karo syrup The nitrogen output included urine only, stools were scanty and when analyzed amounted to but 5% of the urinary nitrogen

hydrate and protein, the total being the same in each case, but insufficient to meet full caloric requirements In one, the proportions were the same as in a normally balanced diet, 80 per cent carbohydrate, 20 per cent protein Nitrogen balance was achieved in three successive periods, but was not very pronounced In the other, the proportions were reversed so that the diet consisted of 80 per cent protein and 20 per cent carbohydrate, nitrogen balance was also achieved, but the degree increased with each succeeding period so that during the last period over ten times as much nitrogen was retained as compared with the last period in the first animal The average nitrogen retained on the high protein, low carbohydrate diet was six times that of the nitrogen retained on the 80 per cent carbohydrate, 20 per cent protein diet, thus, indicating the superiority of an intake consisting largely

of protein, even though the amount of carbohydrate was low. Obviously, such a diet will tend to minimize greatly the tendency toward loss of protein tissue, and adds evidence to the justification for giving priority to protein over carbohydrate when a restricted diet becomes advisable or necessary. Other experiments, however, are in progress.

*Prevention Versus Cure*—The effects of starvation, particularly when they are of long duration, are always difficult to overcome when they concern replacement of lost protein tissue. On the other hand, prevention of protein starvation is relatively simple. Thus, it should be emphasized as a principle of treatment that methods be established immediately after injury or operation to insure an adequate food intake so as to prevent the difficulties which arise when a severely malnourished patient must be treated. Prevention is not only important for this reason, but also because it will combat anorexia, which often persists because of starvation itself. Adequate nutrition from the very beginning, thus, breaks into the vicious circle mentioned above. This means that the surgical patient receives in his oral or parenteral diet at least 50, and preferably 100, grams of protein a day from the first day after operation or injury. Thus we have done and have observed definite alleviation of the above mentioned manifestations due to starvation. Moreover, appetite has returned much earlier, permitting a normal dietary regimen sooner than was previously the case.

#### COMMENT

Acute starvation after injury or operation, while prevalent, should not be viewed with complacency in view of the evidence herein assembled that definite physiologic impairment follows such starvation even of short duration. In most cases this deprivation is confined to caloric or protein needs. While most patients eventually get well in spite of starvation, it is probable that convalescence can be greatly shortened and complications minimized by avoiding such deficiencies. Food is so necessary for life in health that its importance in the injured would seem to be obvious, yet such a fundamental truth often escapes the surgeon in his care of patients after operation or injury.

Although the prevention of starvation can be achieved by insuring an adequate diet either by mouth or parenterally, evidence is presented to indicate that a large part of the caloric needs may safely be sacrificed for short periods without physiologic impairment provided an adequate protein intake is assured. While further observations are required to establish the soundness of this view, its practical importance is sufficient to warrant further studies. Since the caloric component of the diet is by far the largest, the possibility of waiving even a considerable part of it becomes an important consideration, particularly during periods when intravenous feeding is necessary. Such a priority of protein over caloric needs may also be important in war time, when healthy soldiers are deprived of their sources of supply and must subsist for many days on rations containing as little bulk as possible.

Under such conditions it may be more important to insure nitrogen balance with a high protein diet than to provide fat and carbohydrate for all of the caloric needs. Should loss of body weight occur as a result of starvation, clearly it is much more important that nonessential tissue fat rather than essential tissue and plasma protein be depleted.

#### SUMMARY

1 Acute starvation after injury or operation is usually confined to caloric and protein needs, though due to deprivation of these nutritional elements, excessive destruction and loss of protein is an important added factor.

2 Deprivation of protein is serious because it leads to early loss of tissue and plasma protein, deprivation of calories is less serious because it leads primarily to loss of nonessential fatty tissue.

3 The effects of starvation after operation or injury are due largely to protein deprivation and include a variety of mild and serious clinical manifestations. Hypoproteinemia is frequent after operation or injury but is often masked by dehydration or hyperglobulinemia.

4 Starvation may be avoided to a considerable extent by recognizing anorexia as a therapeutic challenge rather than an inevitable symptom.

5 Evidence is presented indicating much of the caloric need may safely be sacrificed provided adequate protein is furnished. In patients unable to take a full diet by mouth or receiving parenteral alimentation, such a restriction may prove of much practical value.

6 Because prevention of starvation is much easier than its cure, adequate nutrition should begin immediately after injury or operation.

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DISCUSSION —DR CHARLES C LUND, Boston Doctor Elman has given us a good summary of the importance of protein in surgical patients We are hearing more and more about this from various sources Dr Arthur Wright's group, and, of course, before that Doctor Ravdin, and many others, have studied it

It came to my attention most strongly through our work on burns I just want to call attention to two quantitative facts that may not be too generally appreciated as yet

One is that, in general, with the slow development of a slight, long-time protein deficit, the plasma protein usually remains pretty nearly normal until there is a great decrease in the body stores, so at times one will find a patient with only a slight lowering in the plasma protein value, who will in fact be greatly depleted

The other point I want to make is that you have to give protein nourishment either by mouth or, if intravenously, by protein digest, because it is impractical to give enough protein in the form of plasma or albumin to make up these deficits You may have noticed in one of Doctor Elman's charts that 500 cc of plasma were given, and had no effect at all on the plasma protein value

The unit of plasma contains about 18 Gm of protein, and the patient, to stay in balance without any great burden of illness, has got to have 75 Gm of protein a day If there is a particular loss or burden, he may need 200 or 300 Gm a day to make it up, and that may have to be done over a long, long time It just is not possible to get enough human plasma or human albumin to do anything more than tide over the greatest emergency for a very short time

I want to emphasize, also, Doctor Elman's statement about the rapidity with which protein stores can be depleted under certain conditions, and the great difficulty of getting them back after they are depleted Some of you will remember that last year I presented a case of burns that lost 50 pounds of weight in a period of about eight weeks The vicious cycle was broken, but after 14 months he had gained back only two-thirds of that loss in weight, and I think we were fortunate that he recovered that much, compared to the known difficulties that exist in repairing such terrific depletions

DR EVARTS A GRAHAM, St Louis, Mo I think Doctor Elman has made a very important contribution in calling attention to this important fact about starvation which may occur right under our eyes

I have been acquainted, of course, with Doctor Elman's work, which led up to this, and also the present work which he has reported here today When he discussed this matter with me a good while ago, I mentioned the fact to him that this is one of those strange phenomena which take place, namely, that it was well known, and has been well known for a long time, that starvation does take place in surgical patients, but that it was something like the weather, and nobody seemed to do very much about it, and I thought it would be an admirable thing for him to do something about

In the work of the Empyema Commission in World War I, Doctor Bell made a particular study of the nitrogen loss in patients with empyema, and his study is included in the report of the Empyema Commission He called attention, at that time, to the great difficulty there was in keeping patients with empyema in nitrogen balance, and emphasized very strongly the importance of feeding these patients generously in order to keep up nitrogen equilibrium and to prevent them from losing weight, and thereby delaying their convalescence

At that time, which was in 1918, 26 years ago, there were no satisfactory methods for studying plasma protein The work had to be done almost entirely by studies of

nitrogen excretion in the urine But that observation was very definite It was clearly established, it was much commented on at the time, it was made much use of, and, as a matter of fact, I have tried ever since that time to emphasize to our own house staff the great importance and necessity of overfeeding patients with empyema in order to keep them from losing weight, with particular reference to the protein

Unfortunately, unless one gives personal supervision to it, it is one of those things that is not done as it should be done, because its importance is not recognized It is necessary, therefore, for somebody like Doctor Elman to come along, using more modern methods, to reemphasize the importance of watching the patient's food requirements, particularly his protein requirements

We realize now, more than we did 26 years ago, that protein requirements are especially important, and, therefore, I am very glad to have Doctor Elman, shall I say, bring up this subject again with new methods, in order to emphasize the whole problem and the importance of it once more

DR PAUL R CANNON, Chicago Doctor Elman, in my opinion, is approaching the problem in the right way in stressing the basic significance of "starvation" in surgical prognosis Surgeons, indeed, have an opportunity to study the surgical effects of starvation and to learn important facts about protein metabolism that may be applied to the treatment of starvation in general, for, after all, considering the fact that millions in India, China, and the occupied countries, are suffering from varying degrees of food scarcity it is probable that starvation is now one of the world's most important diseases

In the field of medicine we must take our material where we find it, therefore, when surgeons are confronted with the facts of starvation it is their duty to study the disease itself

Doctor Elman called attention to the difficulties of evaluating the significance of plasma protein concentrations because of the fact that with a declining albumin concentration and a rising globulin concentration the total protein concentration may remain in the normal range We must recognize the fact, of course, that a blood protein determination reveals only the concentration of protein in the blood at one particular instant, and that it does not necessarily afford evidence of the state of the protein reserves In thinking about the relationship between the plasma proteins and reserve proteins, a rough comparison may be made between the relationship of the level of water in a well shaft and the ground water reserve When the well driller sinks a shaft into two types of soil, one with rich water reserves and the other with low reserves, he determines the state of these reserves by emptying the shaft and seeing how rapidly water comes back to a certain level Similarly, in patients presumably who have lost considerable amounts of blood protein from protein reserves already depleted, the reestablishment of plasma protein concentrations will be slow Therefore, when there is a history of malnutrition and loss of weight before operation one may assume depletion of the protein reserves regardless of the fact that because of the decrease of blood volume a total protein concentration from one determination may not actually reveal the state of the protein reserves



# SYMPOSIUM ON BURNS

## THE HEALING OF DEEP THERMAL BURNS\*

### A PRELIMINARY REPORT

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IN THE TREATMENT of the local area in deep thermal burns the ultimate objective should be the grafting of skin at the earliest moment compatible with success and with a minimum mortality rate. The chief cause of delay in the healing of these wounds is, in effect, the continued presence of the slough. Such dead tissue is essentially powerless to combat infection, with it successful skin grafting is impossible and contracture continues. It is regarded as of signal importance, therefore, to effect the removal of the slough at the earliest moment. The advantage of this removal is fully realized, however, only when the resultant base of the wound is acceptable for immediate grafting with skin, and when there is no significant damage to living tissue.

Enzymatic digestion of the slough in wounds has recently received attention. Glasser (1940) reported success in this connection using a proteolytic compound containing papain. He cited the favorable results obtained in chronic otitis media by Tremble, using urea and caroid in a saturated aqueous solution. More recently, Cooper, Hodge and Beard (1943) reported on the use of an enzymatic digest for the removal of dead tissue. Howes (1943) noted that various enzymatic compounds were effective in removing the slough in wounds in from 24 to 48 hours. Several of these damaged living tissue. Howes also noted that the dead tissue was removed with more difficulty if the enzymatic compounds were first applied after several days.

It is well known that infection often hastens to a certain degree, but at a high price, the separation of the original slough in deep thermal burns. There is the general impression that the hydrogen ion concentration of the wound fluid is increased in many infected wounds, and this has been confirmed in our experiments. The results of preliminary experiments with the local application of various organic and inorganic acids revealed that the separation of the slough could be greatly hastened if the  $p_H$  of the surface of the wound was sufficiently lowered. A large series of acids have been studied in this connection, and it is now apparent that under proper conditions not only does the slough separate more rapidly than in the control wound, but

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\* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Yale University.

Read before the American Surgical Association, May 3-4, 1944, Chicago, Ill

the living tissue is not significantly damaged and the resultant base of the wound is such as to permit successful and immediate grafting with skin

Pyruvic acid presents outstanding advantages within the objectives of this method of treatment. With it the necessary balance between  $p_H$  and concentration of the acid can be obtained in order to accomplish the desired results.

It is the purpose of this report to describe some of the pertinent experimental data concerning the use of this method in the treatment of deep thermal burns.

#### METHOD

Dogs were used, and anesthesia was obtained with intravenously administered nembutal. The hair over the trunk was clipped closely or shaved. Aseptic precautions were not used, and there was no further preparation of the skin.

Deep burns were produced by the direct application of a low blue gas flame to the skin for 20 seconds over the dorsolateral aspect of the trunk. This standard burn was from three to four centimeters in diameter, and uniformly involved the full-thickness of the skin.

In the *control* series the wounds were studied either concurrently with experimental wounds in the same animal, or in separate animals. In the first instance, the control and the experimental wounds were made on similar areas on opposite sides of the trunk, so that each animal served as its own control. In the latter instance, the control wounds were placed on separate animals, to preclude any possibility of their contamination with the solutions used on the experimental wounds.

The control wounds were dressed within a few hours after burning with either dry gauze, vaselined gauze or a paste consisting of 8 per cent cornstarch in distilled water. The dressings were changed every one to four days, and similar dressings reapplied.

The *experimental* wounds were dressed within a few hours after burning with a thick layer of paste consisting of a solution of pyruvic acid at a  $p_H$  of 1.9 and of 8 per cent cornstarch\*. This was prepared by mixing a hot solution of pyruvic acid in distilled water at a  $p_H$  of 1.9 with the necessary amount of cornstarch suspended in a similar but cool solution. This paste was applied thickly on the surface of the wound and the adjacent skin and was held in place with gauze. This inner dressing was then covered with a layer of vaselined gauze. The dressings were changed daily or every two days.

In both the control wounds and the experimental wounds the dressings were securely held in place with an adhesive elastic bandage enclosing the trunk.

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\* It should be emphasized that the starch paste used in these studies was selected in order to avoid a complicated base during this phase of the work. From the standpoint of preliminary experimentation this is satisfactory, but it is not a desirable vehicle from the practical viewpoint. An oil-in-water emulsion is a satisfactory base in this connection.

All animals in which the dressings loosened, with exposure of the wounds, were deleted from this study, whether or not there was any evidence of additional trauma to the wounds. The dressings were carried out usually under light anesthesia with intravenous nembutal so as to eliminate the possibility of trauma to the wounds from the struggling of the animal during the dressing.

The skin grafts were taken from the thigh or trunk of the same animals, and were cut with the Padgett-Hood dermatome set at  $16/1000$  of an inch. The grafts were sutured in place with fine silk or were merely "snubbed" on with pressure. The grafted wound was covered with a layer of *tulle gras*, and a bulky pressure dressing applied.

### RESULTS

*Control Group*—(20 wounds) Whether the control wound is on a symmetrical area on the side of the trunk opposite an experimental wound or on a separate animal, the complete separation of the slough requires from 10 to 12 days. The slough softens on its surface and breaks up into many pieces which are firmly adherent. During the week before complete separation the wound is covered with a necrotic, stringy adherent layer (Figs 1 and 2).

Healing takes place by contracture and by the marginal ingrowth of epithelium, without the appearance of islands of epithelium within the wound. Such a standard burn may, therefore, be classified as a deep one.

*Experimental Group*—(20 wounds) In the experimental series the slough separates completely within 72 hours (Figs 3 and 4).

The manner of separation of the slough under these circumstances is of particular significance. Separation appears to begin at the periphery where, in 24 to 36 hours, there is slight softening. A plane of cleavage develops beneath the otherwise intact slough, and separation proceeds centralwards. After 48 hours the cleavage has developed to the point where the slough, aside from soft dermal tags at the periphery, is either completely free

FIG 1—Control Wound. Standard deep thermal burn on the dorsolateral aspect of the trunk of the dog, five days after burning. Original burn similar to that shown in Figure 3, and produced by the same method. Treated with pressure dressing of dry gauze. Note adherent slough.

FIG 2—Control Wound. Same wound as shown in Figure 1, ten days after burning. Slough separating piecemeal, but still adherent in many areas. Dressings had been changed on the second, fifth, eighth and tenth days after burning.

FIG 3—Experimental Wound. Standard deep thermal burn on the dorsolateral aspect of the trunk of the dog, 30 minutes after burning.  $3.8 \times 3.1$  cm. Burn produced by direct application of a low blue gas flame for 20 seconds.

FIG 4—Experimental Wound. Same wound as in Figure 3, 72 hours after burning. Treated with a daily application of a thick layer of pyruvic acid paste at a pH of 1.9, beginning one hour after burning.

Slough separated completely. Note the clean, healthy base of the wound. Central part of the wound grafted on this day with a split graft cut at  $16/1000$  of an inch, to include an adequate dermal pad. Wound covered with a *tulle gras* and pressure dressing.

FIG 5—Experimental Wound. Same wound as in Figures 3 and 4, five days after burning, two days after grafting of central area. Living graft and healthy granulation tissue.

FIG 6—Experimental Wound. Same wound as in Figures 3-5, 16 days after burning, 13 days after grafting. Note the living graft and epithelial proliferation at the margin of the graft and of the wound. Still no evidence of skin islands in the ungrafted area.



FIG 7—Experimental Wound. Deep thermal burn in the dog, similar to that shown in Figure 3, 66 hours after burning. Treated daily with a thick layer of pyruvic acid paste at a pH of 1.9. Shown to illustrate the manner of separation of the slough, which is completely free beneath and is attached only by soft peripheral dermal tags. The intact central slough is rubbery, without evidence of digestion on the surface.

FIG 8—W. P. N. II H., Unit B4705. Deep fire burn in a four-year-old boy at time of admission to the hospital, one week after burning. Wound had been treated at home with various ointments and signs of local infection had developed. Culture of necrotic tissue revealed hem. Strep., hem. Staph. aureus, gram-negative bacilli and enterococci.

Treated with a generous application of pyruvic acid paste at a pH of 1.9, with the dressing sealed with vaselined gauze. First dressing on the third day after admission at which time 40 per cent of the slough had separated. Similar dressing reapplied on the third and fifth days after admission.

FIG 9—Same burn as shown in Figure 8, six days after admission. Slough completely separated, clean granulating base with unusual vascularity. No evidence of damage to adjacent unburned skin.

The wound was obviously ready for grafting but was treated for an additional four days with the same paste, without evidence of injury to the exposed base. Split grafts applied after this additional treatment, on the tenth day after admission.

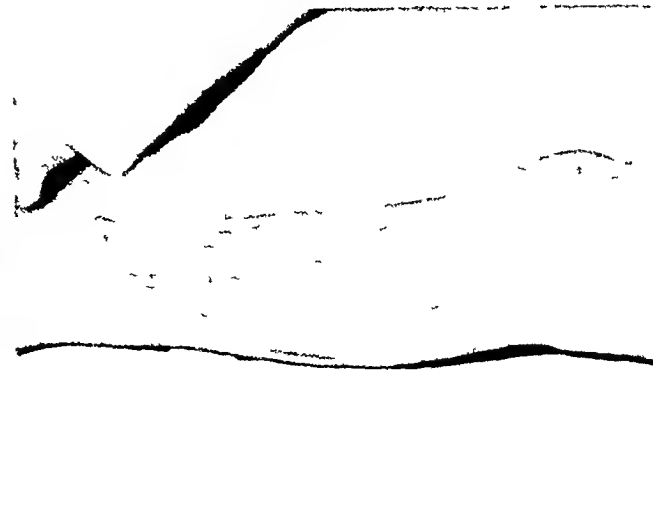
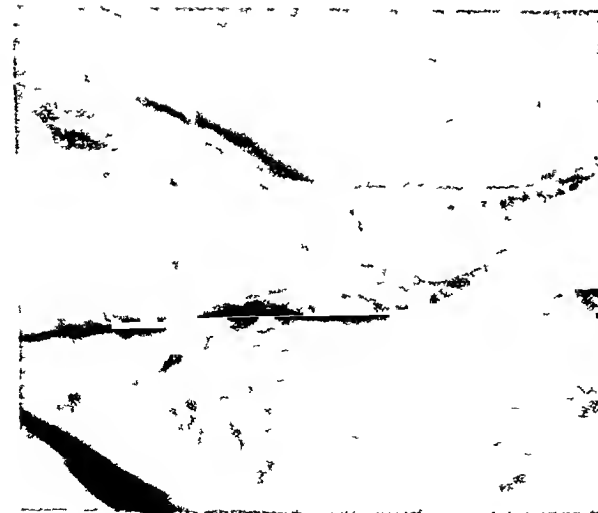
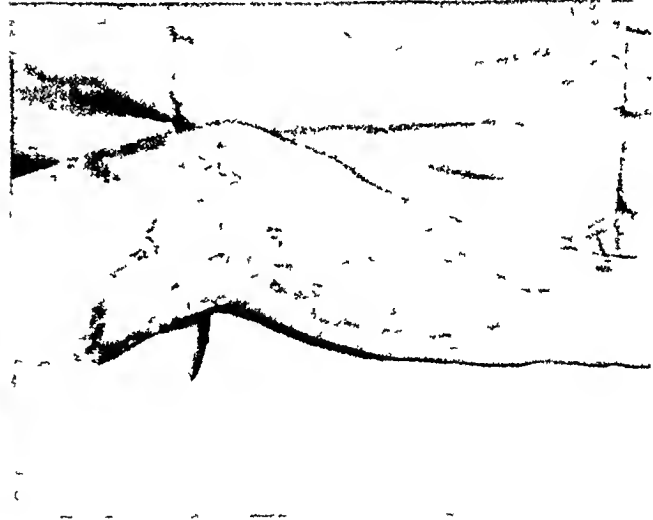
FIG 10—Same wound as shown in Figures 8 and 9, ten days after grafting. The margins of the wound were not trimmed at the time of grafting.

FIG 11—Same wound as shown in Figures 8-10, five weeks after admission, with protective dressings no longer necessary. Patient ambulant.

FIG 12—Opposite side of the same leg, with a burn similar to that shown in Figures 8-11, treated in a similar manner.

Final result five weeks after admission.

7



11



otherwise, or loosely attached beneath its center (Fig 7) In another 12 to 24 hours separation is complete, with the slough lying free in one piece

It is clearly apparent, and is of special importance, that there is no evidence of digestion of the slough itself It is similarly clear that the dermal strands at the periphery of the slough are last to separate, although they are markedly softened for many hours before separation is complete The skin adjacent to the burn appears undamaged

The resultant base is, grossly, pink subcutaneous tissue Within 72 hours after burning, this base is unusually vascular and, histologically, exhibits evidence of early granulation tissue The edges of the wound are sharp and clean, and are often tangential, as would be consistent with the more superficial damage at the very margins

The full advantage of the rapid removal of the slough by this method is demonstrated when the wound is immediately grafted with skin The pink, clean base evident after separation of the slough accepts a split-graft of skin immediately (Figs 5 and 6) This regularly takes, and all or part of the wound may be successfully treated in this manner

The problem of infection is thus resolved, and the full objective of treatment achieved even before the slough in the comparable control wound has completely separated

The utility of this method of treatment of burns would be seriously reduced if with its use residual epidermal elements were necessarily destroyed Such is not the case, however, for in those burns in which the damage extends only into the derma, but with preservation of the deeper epidermal elements, separation of the slough proceeds in such a manner as to permit epithelization from the intact islands of skin Under these circumstances the cleavage plane develops within the derma, and the slough separates more slowly, often requiring an additional 48 hours over that necessary when the cleavage is beneath the derma

DISCUSSION—Rapid removal of the slough can be achieved by the use of any of a large number of acids of various types incorporated in vehicles, the one necessary characteristic of which is a dominant water phase It is important to recognize that this process is not a digestion of the slough, as is the case with the various enzymes previously employed Instead of being broken up into fragments and dissolved, the slough separates as one or more large pieces By this method the establishment of a plane of cleavage between dead and living tissue is accelerated, starting at the periphery, where the delimitation between the two occurs on the surface, and proceeding into the deeper tissues along the same boundary until the separation is complete and the slough so removed This is apparently a speeding-up of the normal reaction to injury and, more specifically, that to dead tissue by means of which this is sequestered and dislodged The mechanism by which these acids bring about this acceleration requires further study

To remove the slough in this manner, without damage to living tissue, requires not only the selection of the proper acid, but also careful and



accurate adjustment of the  $p_H$  and concentration of the acid chosen. When this is done, as shown by these experiments, not only can the dead tissue concerned in complete destruction of the skin be rapidly removed, but this can be accomplished without significant injury to the adjacent and viable epithelial cells. Moreover, when the separation of the slough is completed the base is living tissue, with an excellent blood supply, which will successfully and immediately take a skin graft, or if this is not done, healing of the wound by contracture and epithelization proceeds normally, as in a "cut-out" wound.

It is apparent that if these results can be obtained in the clinic, healing of the more severe burns may be markedly expedited by early grafting, and infection, scar tissue formation with contracture, and the general effects of a persisting open wound can be largely obviated.

The use of this method on man is being studied, but has not as yet been adequately tested, nor has a standardized procedure in all details been adopted. Until these have been done, its application for the purposes of treatment should be delayed.

#### SUMMARY

In the experimental laboratory it has been found that the normal development of a plane of cleavage between living and dead tissues can be markedly accelerated by the use of acids. With certain of the organic acids, in the proper concentration, and with a carefully and suitably adjusted  $p_H$ , this can be accomplished without significant injury to viable tissues.

This makes it possible in the experimental animal to remove the slough resulting from a severe burn in 48-72 hours, and to employ immediate skin grafting for the closure of the wound.

The application of this method to man should wait upon further study and the development of proper methods of application.

The authors wish to express their appreciation to Dr Philip B. Cowles of the Department of Immunology, Yale University, for his invaluable assistance in this study.

Acknowledgment is due to Dr C. N. H. Long of the Department of Physiological Chemistry, for his valuable suggestions.

We wish to thank Mr Howard Reynolds and Miss Mildred Konick for the photography.

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# A STUDY OF THE INTERRELATIONSHIP OF SALT SOLUTIONS, SERUM AND DEFIBRINATED BLOOD IN THE TREATMENT OF SEVERELY SCALDED, ANESTHETIZED DOGS\*

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FLUID THERAPY IS NOW recognized to be fundamental in the immediate treatment of burned or scalded man<sup>6, 11, 12</sup> However, relatively little quantitative data are available concerning the individual physiologic effectiveness and the interrelationship of diverse repair salt solutions, cell-free blood components, and whole blood derivatives in the treatment of controlled thermal trauma The purposes of these experiments are as follows 1 To correlate body loads of various salt solutions and plasma with length of life and changes in other easily measurable physiologic constants that follow a scald, 2 to attempt a comparative evaluation of the relative rôles played by salt solutions, cell-free blood components, and whole blood in permitting immediate recovery from injury (74 to 100 hours following the trauma), 3 to correlate the gross and histologic, pathologic findings with the forms of therapy, and 4, to determine, if possible, whether or not any causal relationship exists between the type of therapy and the so-called "toxemic" stage of thermal injury.

## METHODS

Seemingly healthy, adult mongrel dogs of both sexes were anesthetized solely with sodium evipal (1 methyl, 5  $\Delta$  ' cyclohexenyl 5 methyl barbiturate) Fifty milligrams of a 5 per cent aqueous solution per kilogram body weight were injected intravenously as the initial dose, subsequently, a very light anesthesia was maintained for 14 to 20 hours by the administration of appropriate doses Precautions were taken to provide a free air-way Direct, mean, lateral arterial blood pressures were obtained in two-thirds of the experiments by femoral arterial puncture The animals were scalded by immersion of two-thirds of the body in water at 85° C for 30 seconds The dogs were not clipped, since clipping was found to diminish the injury Samples of venous blood were taken from the femoral, antecubital or jugular

\*A preliminary report concerned mainly with purposes 1 and 2 (see page 1 of the text)

Aided by a grant from the Horace H Rackham Fund

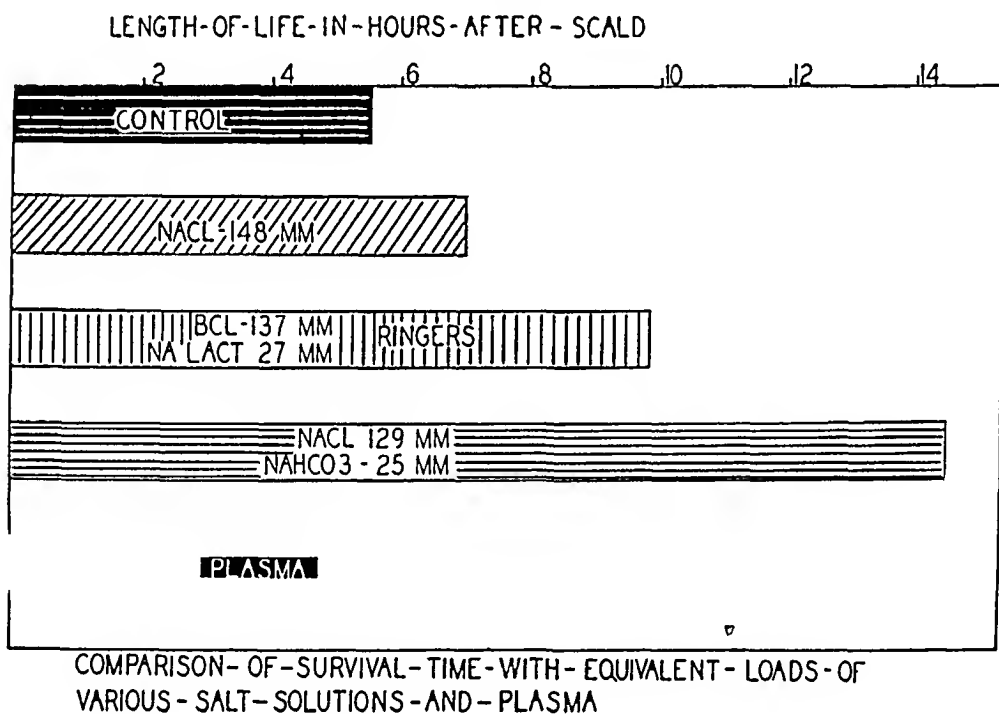
Read before the American Surgical Association, May 3-4, 1944, Chicago, Ill

veins† Heparin was used as the anticoagulant The hematocrits were determined immediately by the capillary tube method The specific gravities of whole blood and plasma were determined by the "falling-drop" method<sup>2</sup> The plasma protein values, with the exception of the saline series, were corrected for hemoglobin, and micro-Kjeldahl checks<sup>9</sup> of the values of protein calculated from the specific gravities of the plasma were run Hemoglobin was determined by the Evelyn method,<sup>7</sup> using the 20-c mm pipette of the falling-drop method Urine was collected by a cystotomy tube or by a small urethral catheter inserted through an external urethrotomy in male animals, and by an indwelling flanged retention catheter in females

## RESULTS

Chart I and Table I show the mean survival time of the control group and of those animals loaded before the scald with physiologically equivalent amounts of (1) isotonic sodium chloride\* ( $\text{NaCl}$ , 154 mM), (2) Ringer's-

CHART I



lactate (Ringer's, 137 mM base + Na lactate, 27 mM), (3) saline-bicarbonate ( $\text{NaCl}$ , 129mM +  $\text{NaHCO}_3$ , 25mM), and (4) citrated plasma‡

The difference in survival time after the scald between the controls and the animals loaded with the physiologically acid, "isotonic" sodium chloride

† Simultaneously obtained samples from the jugular and femoral veins before and after the scald showed no significant difference

\* 50% of the volume of distribution of sodium thiocyanate (10% body weight)

‡ 50% of the volume of distribution of the dye T-1824 (2.5% body weight) Because of the severe citrate reactions which could be controlled only with injections of  $\text{CaCl}_2$  solution i.v., serum was used in all subsequent experiments

is insignificant (critical ratio = 0.9) ‡ However, the animals loaded with Ringer's-lactate lived significantly longer than the controls and the saline group (critical ratio = 5.2), and those loaded with saline-bicarbonate lived longer than did all the other groups NaCl-NaHCO<sub>3</sub> *vs* controls (C R =

TABLE I  
SURVIVAL TIME OF CONTROLS AND DOGS LOADED BEFORE SCALD

Treatment	No of Dogs	Mean Survival Time		Standard Error Minutes	Standard Deviation Minutes	Critical Ratio*
		Hours	Minutes			
Controls	7	5	21	±31	81	
0.9% NaCl, 10% body weight*	5	6	50	±94	210	0.9
NaCl—Na lact, 10% body weight*	7	9	37	±38	92	5.2
Citrated plasma 2.5% body weight†	4	9	5	±32	64	5.1
NaCl—NaHCO <sub>3</sub> , 10% body weight*	4	14	12	±44	88	9.9

\* 50% volume of distribution of sodium thiocyanate  
† 50% volume of distribution of the dye T-1824  
± A critical ratio of 3.3 or more indicates a true difference in 999 cases in 1000

TABLE II  
Immediate Treatment During First 24 Hours,  
Per Cent, Body Weight

Animal No						Survival Time Hours	Cause of Death
	Blood	Serum	NaCl NaHCO <sub>3</sub>	Route Fluid	H <sub>2</sub> O Ad Lib		
39	0	0	25	iv	0	24	Shock pulmonary congestion
40	0	0	30	iv	0	25	Shock
41	0	0	30	iv	0	25	Shock
43	0	0	12	iv	0	3	Acute cardiac failure
42	0	5.0	28	iv.	0	52	Pulmonary congestion
44	0	3.5	28	iv	0	23	Pulmonary edema and congestion
45	0	3.8	23	iv	0	31	Pulmonary edema and congestion
46	0	4.5	15	iv	0	29	Acute pulmonary edema
48	0	1.6	5	iv	0	28	Shock
64	0	5.0	6	oral	0	10	Pulmonary edema
65	0	5.0	3	oral	0	20	Pulmonary edema
66	0	6.0	5	oral	0	70	Pulmonary edema and pneumonia
60	3.6	0	0	—	5.5	50	Brain and pulmonary edema
61	3.4	0	0	—	10.0	92	Brain edema pulmonary con- gestion
62	3.5	0	0	—	5.0	34	Brain edema
63	3.5	0	0	—	0	19	Shock, pulmonary congestion
56	2.5	0	8	oral	0	35	Distemper
57	2.2	0	15	oral	0	76	Sacrificed negative autopsy
58	2.7	0	11	oral	0	100	Sacrificed negative autopsy
59	5.1	0	13	oral	0	100	Sacrificed negative autopsy

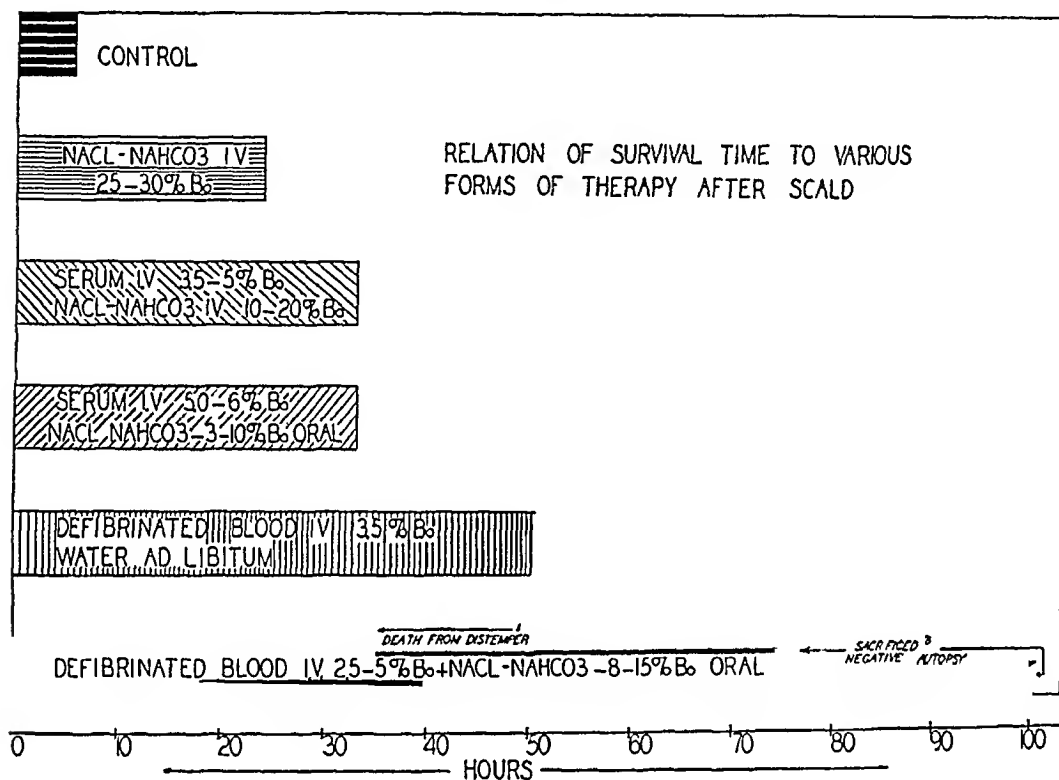
9.9), *vs* saline (C R = 4.3), *vs* Ringer's-lactate (C R = 6.5), and *vs* citrated plasma (C R = 5.6)

Following the "load" series of experiments, a comparative study of therapy was undertaken Chart II shows the effects of various forms of therapy upon the survival time The relation of the various forms of therapy to survival and the causes of death based upon the gross pathologic findings are shown in Table II

‡ Critical ratios of 3.3, or more, are significant

DISCUSSION—In order to apply the principles of bio-assay to the study of the relative effectiveness of various salt and blood elements in treating small series of scalded animals, it is theoretically necessary that the extent and the depth of the injury should be of such a degree that death will occur in all the animals of all series, excepting one. Upon that basis, an injury

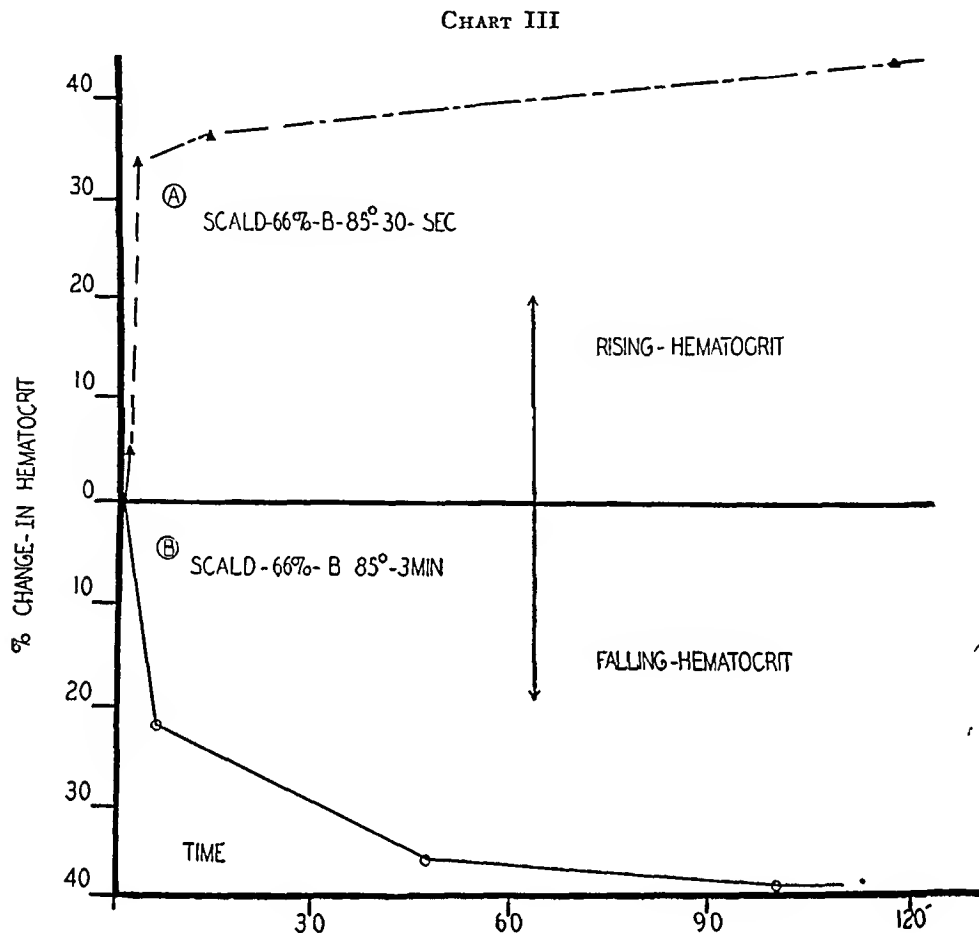
CHART II



that killed within three hours would be more desirable than one that killed within six hours. However, although a scald produced by the immersion of two-thirds of the body surface in water at 85° C for three minutes kills within three hours, it produces a picture which is unlike the majority of thermal injuries seen in man (Chart III). Compare the hematocrit change A (85° C for 30") with B (85° C for 3'). Therefore, the scald produced by water at 85° for 30 seconds, although it killed in a little over five hours, was chosen as the means of producing a relatively constant thermal trauma against which the various solutions were assayed.

The series of experiments in which the test solutions were injected before the scald in equivalent physiologic amounts show that a positive load of the physiologically acid solution of isotonic sodium chloride has practically no propensity for prolonging life after a severe scald. A load of Ringer's solution to which sodium lactate has been added to make a fluid osmotically equivalent to the isotonic salt solution significantly increased the length of life. Was it the addition of the cations Mg and K or the addition of the

anion  $\text{HCO}_3^-$  that effected the change? The increased survival time in the next series of experiments (preburn loading with sodium chloride-sodium bicarbonate) shows that if the cations exert any effect it is small when compared to the anion  $\text{HCO}_3^-$  effect (the  $\text{HCO}_3^-$  equivalency of the  $\text{NaCl-NaHCO}_3$  solution is physiologically double that of the Ringer's-lactate solution)



Loading with plasma was surprisingly ineffective. From one-fifth to one-half of the protein that was injected disappeared from the blood stream within the hour and an half which was allowed to elapse between the completion of the injection and the scald.

No experiments were conducted using M/6 sodium lactate as the preburn load because of its adverse effects upon the acid-base equilibrium and its obviously extensive constitutional difference from interstitial fluid\*. The administration of this solution in large amounts would make the transfusion of citrated plasma or blood extremely hazardous and, if renal function was depressed, would effect alterations in the relationship between interstitial and cell fluid that must be considered as physiologically undesirable.

The significant superiority of saline-bicarbonate as a repair solution in thermal injury is somewhat surprising in view of prevalent opinion,<sup>6</sup> and other experimental work<sup>10</sup>. However, it is in agreement with general

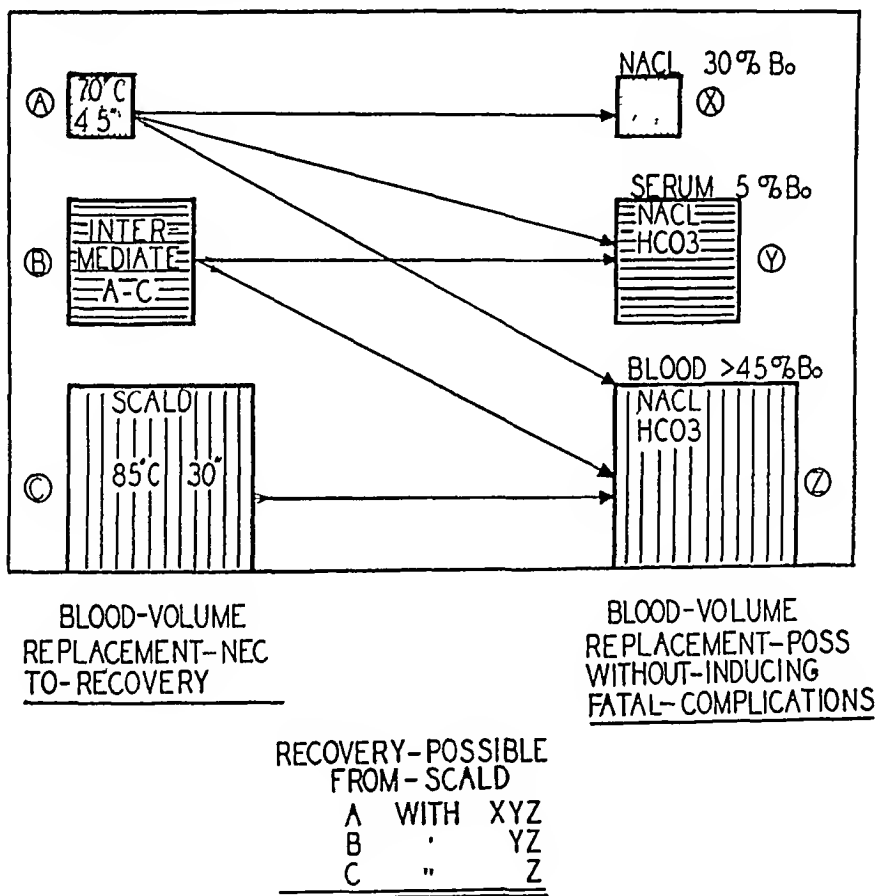
\* Unpublished data

physiologic knowledge that the more nearly a solution approximates the composition and reaction of the normal body fluids, the more satisfactory it is for studying living tissues *in vitro*

The results of the second series of experiments show that saline-bicarbonate, when administered intravenously after the scald to 30 per cent of body weight, prolonged life but did not prevent an hypotensive death. The injections of these large amounts of saline-bicarbonate were attended by

CHART IV

THEORETICAL-RELATIONSHIP-OF-VARIOUS-TYPES-OF  
THERAPEUTIC-AGENTS-TO-SEVERITY-OF-THERMAL-INJURY



profound, persistent, and disproportionally great depressions of the plasma proteins and the rapid development of massive subcutaneous edema in the scalded area. Saline-bicarbonate does not differ from isotonic, intravenous saline in this respect<sup>3</sup>

The intravenous injection of both saline-bicarbonate and serum either killed (by inducing acute pulmonary edema and pulmonary congestion), or the amounts given were inadequate. In other words, any amount of both fluids that was less than that which produced pulmonary or cardiac complications would not prevent death from "shock." As a result of observations

made during the saline-bicarbonate and the saline-bicarbonate-serum series, it was decided that the only "safe" way to give salt solution during the acute stages of thermal injury was *via* a route whereby the rate of entrance of the solution into the blood stream was controlled by the animal, namely, by stomach, by rectum or subcutaneously. The saline-bicarbonate solution in all the later experiments was given by stomach catheter (Table II). Absorption of saline-bicarbonate to the extent of 10 to 13.5 per cent of body weight usually took place within 12 hours.

The three animals that were treated with serum by vein (5 per cent of body weight within 13 hours) and sodium chloride-bicarbonate solution by stomach tube died of pulmonary edema, two within 24 hours and one within 70 hours. The latter showed clinical signs of pulmonary edema throughout her life, and at death the edema had progressed to an extensive hepatization of four-fifths of both lungs.

Defibrinated whole blood without saline-bicarbonate effected temporary recovery, but all the animals in the series died within 70 hours of the scald. This agrees with the observations of Williams, Eghart and Trusler.<sup>13</sup> Twenty-four hours after the scald three animals out of four had fully recovered from the anesthesia. They were walking easily about their cages without signs of pain, and they drank large amounts of water when it was given to them. Shortly after drinking the water (2 to 20 minutes) they began to vomit and to have a bloody diarrhea. Thereafter, they continued to drink, to vomit and to defecate until too weak to drink. Fibrillary twitching of all muscle groups appeared when they were unable to get up, and they died suddenly, howling and in convulsions. After death their brains bulged over the edges of the skulls after removal of a bone flap, and fluid dripped from the cut surface of the cerebrum. The general appearance and behavior of these animals could be called "toxemic." These observations lead us to believe that in the absence of infection, the "toxemic" stage of burns may be largely the result of cellular "overhydration" associated with hypotonicity of extracellular fluid in the uninjured portions of the body. Indirect support for this concept is provided by the lack of these signs within a period of 100 hours (longest time elapsed before sacrifice) in animals treated with blood and oral isotonic saline-bicarbonate during the first 24 hours and hypotonic saline-bicarbonate, in as large amounts as the animals would drink, during the second 24 hours (Table II).

The only form of therapy that is capable of carrying these scalded animals (two-thirds body surface, 85° C for 30") through the "shock" period *without inducing physiologic changes that may in themselves result in death* in less than 100 hours (four days) is a combination of *defibrinated whole blood* intravenously and sodium chloride-sodium bicarbonate by mouth (Table II).

We have no assurance that citrated or heparinized blood will be as effective as defibrinated blood. The work of Ivy,<sup>8</sup> and Graham,<sup>5</sup> suggests that citrated blood may be found to be inferior and may even be detrimental.



Heparinized blood, should it act similarly to heparinized plasma, will increase the escape of red cells into the area of injury \*

It has been interesting to find that an hematocrit of 75 to 80 per cent that was maintained for 8 to 10 hours, in scalded animals, given massive transfusions of defibrinated blood, is compatible with life, provided that sodium chloride-bicarbonate is also given by stomach. Hence, even the hemoconcentration of severe thermal injury does not contraindicate the transfusion of whole blood, if the general physiologic state of the animal requires it. No gross cardiac or circulatory abnormalities were associated with the high hematocrit, and no significant, gross pulmonary, hepatic, renal, cerebral, splenic, or mesenteric infarcts were seen at autopsy following sacrifice of the animals. These observations substantiate Darrow's<sup>6</sup> comments regarding the transfusion of whole blood in the treatment of the shock of burns, and agree with those made by the British Army Medical Corps during the Libyan Campaign (Col F G Gillespie, personal communication.)

The amount of saline-bicarbonate, in conjunction with defibrinated blood, that is needed to balance the negative load of interstitial fluid imposed upon the uninjured portions of the body by the injury cannot be clearly defined. By using multiple indirect methods that will be described in a separate article, the negative loads of interstitial fluid imposed by the scald in these series of experiments was from 3 to 7 per cent of body weight within 30 minutes after the scald and from 10 to 18 per cent of body weight within 24 hours after the scald. In general, the negative load of interstitial fluid is directly proportional to the inevitable, although variable edema.

It must be remembered that the washing-out of protein from the blood into the scalded tissues and the very rapidly developing and massive edema that attend the intravenous administration of sodium chloride or saline-bicarbonate solutions during the first 24 hours after injury, make the intravenous route unsuitable for the reduction of the acute negative interstitial fluid load. In fact, it is theoretically possible that any salt solution given intravenously immediately following a scald may actually accentuate rather than diminish the physiologically functional negative load of interstitial fluid.

The major clinical generalization regarding the therapy of thermal injuries that can be drawn from these experiments has been stated very clearly by Allen,<sup>1</sup> namely "Ever since the first introduction of the colloid concept, physicians and experimenters have concentrated on treating the blood instead of the patient."

In general, if these experimental observations are valid for all mammals, the therapy of a thermal injury should be directed toward two primary goals. First, blood volume must be maintained at a level that will prevent death from "shock." In the case of a relatively minor injury, this can be done with interstitial fluid alone,<sup>10</sup> serum alone,<sup>10</sup> and presumably with whole blood alone. However, in the case of a severe injury such as obtained in our experiments, defibrinated blood is the only substance tested that is capable

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\* Unpublished data

of maintaining a blood volume compatible with life without inducing lethal complications Chart IV is a theoretical diagram illustrating the relationship of therapeutic measures to the constitutional severity of the injury Second, the negative load of interstitial fluid induced by the injury must be reduced preferably to zero During the acute stage of the injury, this can be done most safely by administering a salt solution which approximates normal interstitial fluid by a route other than the intravenous

#### CONCLUSIONS

1. Saline-bicarbonate solution is more effective than Ringer's-lactate solution, and Ringer's-lactate solution is more effective than "isotonic" sodium chloride solution in prolonging life of anesthetized dogs when 10 per cent of body weight of these solutions is given intravenously before the animals are scalded (two-thirds body surface at 85° C for 30 seconds) The presence of the bicarbonate ion or the potential bicarbonate ion in the lactate solution appears to be responsible for the superiority of the Ringer's-lactate and the saline-bicarbonate solutions

2 The combination of massive transfusions of defibrinated blood and saline-bicarbonate solution by stomach was the only form of therapy employed that prevented shock without inducing complications that were incompatible with life

3 The other forms of therapy employed, namely (1) Saline-bicarbonate, iv, (2) saline-bicarbonate iv and serum iv, (3) serum iv and saline-bicarbonate by stomach, and (4) defibrinated blood iv and water *ad libitum*, prolonged life and in a number of instances prevented shock But all the animals that did not die of shock during the first 24 hours died later of complications that seemed to be related to the therapy rather than to the trauma

4 An hematocrit of 80 to 85 per cent does not prohibit the use of transfusions of whole blood

The authors wish to express their indebtedness to Dr Kenneth N Campbell who prepared the tables and graphs, and to Mr William Troy whose technical assistance has been deeply appreciated

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# A COMPARISON OF VARIOUS TYPES OF LOCAL TREATMENT IN A CONTROLLED SERIES OF EXPERIMENTAL BURNS IN HUMAN VOLUNTEERS\*

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THE INTENSIVE STUDIES which have been carried out in recent years have led to a fair degree of standardization of certain aspects of the care of burns, notably in the prevention and treatment of shock and also of the severe metabolic derangements which may appear later in the course. A greater degree of confusion exists, however, with regard to the local treatment, for, here, certain quite obvious factors have prevented accurate comparisons of even the most promising of the very considerable number of methods which have been brought out or reemphasized from time to time. Thus, it is obvious that no two individual burns, nor any two series, unless both include large numbers of cases, are exactly comparable due to discrepancies in size and severity of the burns and wide variations in age, sex and condition of nutrition in the patients. Nor do experiments in animals offer a better solution of the problem since the local reaction to heat sufficient to cause a burn differs somewhat from species to species and in none does the vesiculation appear which is so prominent a feature of second degree burns in the human.

Certain attempts have already been made to obviate this difficulty by using various portions of a burned area or different regions of the body in a single patient for comparing results of different types of local treatment. Such a method is obviously quite crude when one considers variations in depth of the burn as well as the definite, though small, differences in normal healing rate in various parts of the body. In 1943, Cannon and Cope<sup>1</sup> suggested the use of Thiersch graft donor sites which could be divided into parts for testing two or more agents on the same lesion. While their results indicate that this is a useful method for comparing substances of different modes of action such as a bland ointment and an escharotic, it is subject to certain drawbacks. Thus, it is difficult to cut a graft of exactly the same thickness throughout. And, perhaps, more important is the fact that local agents applied at one limit of such an area may exert an influence to some degree on the neighboring regions or even on the extremes. Finally, although histologically akin, a split-thickness donor area does not simulate a burn exactly because of the different mechanics producing the tissue damage.

We have, therefore, produced bilateral, symmetrical burns in human volunteers for comparative studies of various agents, using a simple apparatus

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\* Read before The American Surgical Association, May 3-4, 1944, Chicago, Ill

consisting of a hollow metal plate of almost exactly ten square centimeters area through which live steam is passed. When such a device, of constant temperature and area, is applied to symmetrical points on the anterior aspect of the thighs for the same length of time, as determined by an electric timer by which tenths of seconds were easily measured, we believe the resulting burns should be very nearly alike in every way, including depth. As will be noted later, also, the burns were very much alike from individual to individual but it was early found necessary to vary the time slightly in the case of women since the few who were included sustained deeper burns than were produced by application of equal duration in males. Cornell University Medical students made up most of the volunteers, and ranged in age from 21 to 26 years.

As proved by biopsy, the fluorescein test,<sup>2</sup> and the nature of the subsequent healing process of uncomplicated lesions, these areas were deep second degree burns, epithelization being accomplished from viable epithelium remaining in hair follicles, sweat ducts and sebaceous glands. Without fail, all lesions showed vesiculation in 24 hours (Fig. 1). It should be mentioned that skin areas to be burned were routinely prepared with iodine and alcohol save in a few instances where the areas were purposely left in a normal state of contamination.

For the first 24 hours following the production of these lesions dry sterile gauze was used as a covering, secured by adhesive tape, completely closing the areas, and the subjects were ambulatory throughout the subsequent course of therapy. The 24-hour delay before definitive therapy was chosen in order to simulate accidental burns, since these are frequently seen after some time had elapsed.

#### EXPERIMENTS

Following removal of the initial dressing, all vesicles were opened using sterile technic, and the areas were débrided in the majority of instances. Routine cultures were taken at this time. One burn was then selected at random for definitive therapy with one agent, and the contralateral area was used as a control, a different therapeutic preparation<sup>1</sup> being employed. A total of 82 burns in 41 subjects were thus available for study.

The effect upon healing of 12 substances of which three were escharotics, was compared and the observations made on the rate and mode of healing and the final result. The end-point was arbitrarily chosen as the time at which epithelium covered the entire area.

*Sulfafilm*—In the majority of cases a film\* was employed as a control as it is the therapy of choice for second degree burns in this clinic and we are interested in obtaining objective comparison with other more common types of local burn treatment. The film used was essentially of two types which we designated as "new" and "old" films. Both were made of a methyl cellu-

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\*A generous supply of sulfafilm was furnished by the manufacturers, Wallace and Tiernan Products, Inc., Belleville, New Jersey.

FIG 1



FIG 2

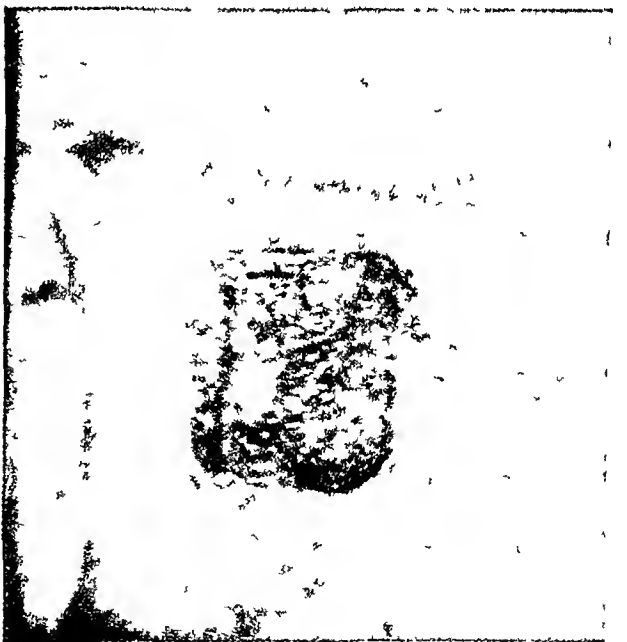


FIG 3

FIG 4

FIG 1 —Bilateral, symmetrical blisters 24 hours following burns. Note the similarity between the two sides.

FIG 2 —Tannic acid eschar intact, showing swelling, redness and inflammatory reaction surrounding lesion six days after application. Patient was complaining bitterly of local pain and had inguinal adenopathy.

FIG 3 —Contralateral burn in same patient as shown in Figure 2. Note absence of reaction.

FIG 4 —Tannic eschar removed on 12th day with no healing evident. Granulations are prominent, suggesting conversion to deeper burn. Inflammatory reaction is still present around the lesion.

FIG 5

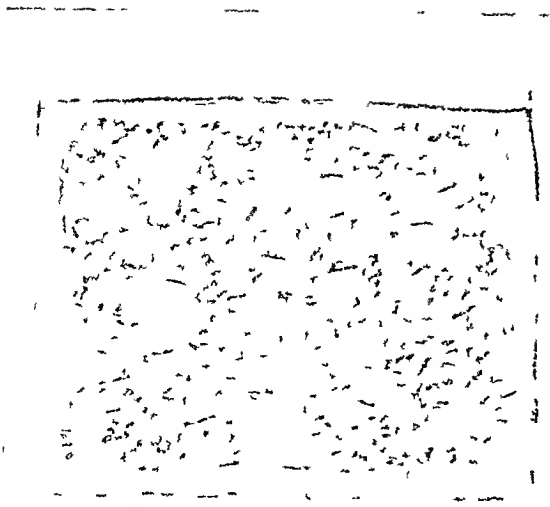


FIG 6



FIG 7



FIG 8

FIG 5—Borie ointment treated lesion on 6th day. Note prominence of epithelial islands with surrounding granulations.

FIG 6—Sulfonamide film treated control in same patient shown in figure 5. Note coalescence of epithelium as compared to discrete islands in borie treated lesion.

FIG 7—Triple dye eschar intact on 7th day with little surrounding reaction. Control (sulfonamide film) healed.

FIG 8—Same patient as in Figure 7 showing conversion to deeper burn after painful removal of triple dye on the 12th day. Control (sulfonamide film) healed five days before.

lose, triethanolamine base into which either buffered sulfanilamide 10 per cent was impregnated or a combination of the former in a concentration 10 per cent and sulfacetamide 15 per cent, making a total of 3 mg of sulfonamide per square centimeter of film. In principle, the film was a "preformed, bacteriostatic eschar," liberating sulfonamide locally on exposure to aqueous fluid. It was transparent, allowing visualization of the underlying surface without removal, pliable, 0.004 inches thick, the film was buffered in order to maintain the surrounding media at a  $pH$  of approximately 8.5. This agent was applied in one or more layers to 42 lesions, the opposite side being treated with one of the substances mentioned below. The average healing time for all uncomplicated second degree lesions treated with film was 9.6 days, but certain aspects of this figure require explanation which will be presented later. Not included in the average are four areas similarly treated, two of which were on female subjects who sustained considerably deeper burns than the males because of the different skin thickness. One lesion was inoculated with *hemolytic Staphylococcus aureus* (in an overwhelming dose) and it became grossly infected within 48 hours, the subject having chills, fever and malaise. Hot wet dressings were applied and subsequent bland ointments. The fourth was one of three subjects who had received two consecutive burns on both thighs. Following application of the film for the second time he developed a severe dermatitis, about which more will be said later.

*Tannic Acid*—Tannic acid was applied to five areas in the form of tannoid ointment\* which was left on for 48 hours, at which time a characteristic firm, leathery eschar was present. In two additional instances a solution containing five per cent tannic acid and five per cent silver nitrate was used. This was applied continually until a firm eschar was formed.

TABLE I  
HEALING TIME WITH TANNIC ACID PREPARATIONS AND CONTROLS

	Tannoid	Control (Sulfafilm)
No 1	27 days	14 days
No 2	24 days	13 days
No 3	22 days	13 days
No 4	16 days	11 days
No 5	14 days	7 days
	Tannic Acid— Silver Nitrate	Control (Sulfafilm)
No 1a	24 days	8 days
No 2a	21 days	11 days

In Nos 1, 2, 3, 5, 1a and 2a there was characteristic reddening, tenderness, swelling and inguinal adenopathy, with gross infection present under the eschar in No 1 and No 5. The eschar was left intact in most instances for about nine days, but in one case it remained for 16 days, at which time

\* The qualitative formula was tragacanth USP grade (extra select), glycerin USP, methiolate solution 1:1000, 95 per cent alcohol, distilled water and tannic acid to 5 per cent of whole.



the lesion was healed (No 4) In all others granulation tissue was present, but the areas subsequently healed by epithelization from scattered foci of glands and ducts All subjects complained bitterly of these areas in contrast to the controls (Figs 2, 3, and 4)

*Boric Acid Ointment*—In five cases ten per cent boric acid ointment was used as definitive therapy, being applied to the débrided burns in mesh gauze and covered with more gauze as pressure dressings Healing time of the lesions thus treated and those of the controls are shown in Table II

TABLE II  
HEALING TIME WITH BORIC OINTMENT AND CONTROLS

	Boric Acid Ointment	Control (Sulfafilm)
No 1	26 days	16 days
No 2	16 days	14 days
No 3	18 days	14 days
No 4	21 days	14 days
No 5	15 days	11 days

Subjects on whom boric acid ointment was used reacted favorably they had no pain, little reaction, and could not distinguish symptomatically between the two sides

*Boric Acid Ointment—Sulfadiazine by Mouth*—Five areas were also treated with boric acid ointment in the same manner as that described above, but during the full course of treatment the subjects were given sulfadiazine, 1 Gm five times a day by mouth, with adjuvant alkali therapy of 2.5 Gm of sodium bicarbonate with each dose<sup>3</sup> All had satisfactory sulfa levels throughout treatment (from 5.5–8.0 mg %) and none had toxic reactions to the drug save headache in three cases

TABLE III  
HEALING TIME WITH BORIC OINTMENT AND CONTROLS

	Boric Acid Ointment Sulfadiazine by Mouth	Control (Sulfafilm)
No 1	13 days	8 days
No 2	12 days	7 days
No 3	7 days	7 days
No 4	8 days	7 days
No 5	9 days	7 days

In this group, although there was a similarity in healing time of contralateral sides, there was a rather noticeable difference in the character of epithelial regeneration As has been said, in all burns healing was accomplished by the growth and spread of discrete epithelial islands from hair follicles, ducts and glands If the ointment-treated side was compared at a near-healing point with the film-treated control, it was noted that in the latter the epithelial "mushrooms" were more flattened, more coalescent, and looked more like mature skin than did that of the ointment-treated side where the islands of epithelium appeared as discrete, shiny noncontiguous rests (Figs 5 and 6) The resultant scar of the latter also required a longer time to assume the characteristics of normal skin

The explanation of this difference is somewhat obscure. We believe that the mechanical feature of the glass-like film in contact with the sprouting epithelium under some pressure may exert a flattening influence causing more rapid coalescence among the islands, whereas, in the other instance the new epithelial buds may protrude between the meshes of the gauze. It is interesting to note in this connection that the size of the mesh spaces and the epithelial islands nearly coincided. The influence which sulfadiazine may have played in shortening the healing time of boric ointment treated lesions will be discussed later.

*Triple Dye*—In four instances a second type of escharotic, triple dye,\* was used. This was applied to the débrided burn areas with cotton swabs until a firm light eschar was obtained. On the whole, such eschars were tolerated better than those obtained with tannic acid, there being very little reaction around the lesions, and no subjective symptoms save continued apprehension on the part of the subject as to whether "infection was developing," especially after the control areas were healed (Fig 7). The eschars were removed, *with difficulty*, by sharp dissection, and with marked pain in from 19 to 28 days (Fig 8). In one case the eschar was left to slough itself, which it did in 31 days, following three or four days of baths. At this time the burn in question was 90 per cent healed, requiring an additional seven days. Healing time for these experiments with their control in the same individual is shown in Table IV.

TABLE IV  
HEALING TIME WITH TRIPLE DYE AND CONTROL

	Triple Dye	Control (Sulfafilm)
No 1	29 days	8 days
No 2	31 days	9 days
No 3	45 days	11 days
No 4	38 days	8 days

At first glance, it will appear that the healing time of the dye treated lesions was longer than that of tannic acid preparations. It should be stated, however, that because of the reaction, tenderness and general distaste for the tannic eschar, they were removed earlier than those of the better tolerated triple dye. The lesions in all instances of escharotic treatment which were not healed on removal of the eschar were treated with bland ointments or adult animal tissue extract<sup>4</sup> until finally epithelized.

*Control Film*—Since we were desirous of knowing what part, if any, the presence of sulfonamides in the plastic film played in the apparent efficacy of this type of treatment, five areas were treated with a control film similar in substance to sulfafilm but without sulfonamide present. Healing times for these lesions are shown in Table V.

\* Aniline gentian violet, 2%, brilliant cresyl green, 1%, neutral acriflavine, 0.1% in 70% alcohol.

TABLE V

HEALING TIME WITH FILM CONTAINING NO SULFONAMIDE

	Film without Sulfonamide	Control (Sulfafilm)
No 1	15 days	10 days
No 2	15 days	11 days
No 3	10 days	7 days
No 4	11 days	10 days
No 5	17 days	12 days

Of interest in the above comparison is the fact that although on original culture both the treated and control areas showed no growth of organisms, in three of the five areas which were tested with the blank film positive cultures subsequently developed, whereas, no positive cultures were obtained from the sulfafilm-treated lesions. It is possible that this may be responsible for the delayed healing time, for in two instances frank infection occurred under the film without sulfonamide.

*Vaselined Gauze*—Four areas were treated with vaselined gauze and pressure without any sulfonamide by mouth. Comparison is shown in Table VI.

TABLE VI

HEALING TIME WITH VASELINED GAUZE AND CONTROLS

	Vaselined Gauze	Control (Sulfafilm)
No 1	26 days	11 days
No 2	7 days	7 days
No 3	8 days	8 days
No 4	20 days	7 days

It should be noted again that although all areas treated with vaselined gauze were negative on original culture, Nos 1 and 4 subsequently became infected, both with *hemolyticus Staphylococcus aureus*, and treatment with the neutral petrolatum had to be discontinued. In two instances no infection occurred, and the healing time compared favorably with that of the control.

*Triethanolamine-Sulfadiazine with Methocel*—This preparation was applied to one area with the control in the same subject being sulfafilm. Healing times were 21 days and 12 days, respectively. Although estimated to be an escharotic of sorts, the triethanolamine-sulfadiazine-methocel preparation failed to produce an eschar in 48 hours.

*Penicillin Ointment*—An ointment of penicillin containing 150 Oxford units per gram was used in one case. The area was not dressed for five days, at which time because of extreme burning, pain and itching the dressing was opened. The area was inflamed, pitted with tender granulations, and showed isolated areas of infection. Further, the surrounding normal skin was excoriated, ulcerated and tender. Further treatment with this method was discontinued. Subsequent healing time of the converted lesion was 34 days. The control area (sulfafilm) was healed in eight days.

*Fibrin Film* —In two instances a plastic film containing human fibrinogen was used. In one of these sulfadiazine was present and in the other there was no sulfonamide (Table VII)

TABLE VII	
HEALING TIME IN DAYS	
Fibrin Film with Sulfadiazine	Control (Sulfafilm)
7	7
Fibrin Film without Sulfadiazine	Control (Sulfafilm)
18-20	11

Gross infection occurred under the fibrin film which did not contain sulfadiazine

*Sulfadiazine-Gelatin* —A preparation of sulfadiazine containing both soluble sodium salt and insoluble sulfadiazine dissolved and suspended in a gelatin base was used in three cases. The resultant mixture was semisolid at room temperature, but on heating became semiliquid. This was painted on the burn area in three cases. Healing times were 11, 7 and 9 days, respectively, as compared to sulfafilm-treated control areas which healed in 13, 8 and 11 days. As a practical burn treatment, however, technical difficulties were encountered. A rubbery eschar was obtained in 20 to 30 minutes after application, but this partially dissolved when serum from the burned area contacted the water-soluble gelatin. For the small areas so treated this was overcome by sealing the gelatin eschar with cellophane and collodion. The resultant dressing remained intact for the time necessary for healing. Such a dressing, however, would be technically impractical for burns involving large areas of the body.

COMMENT

Aside from the comparison between bilateral burns in the same individual, some interesting observations were made in the burns of different subjects which were treated by a similar agent. Naturally, at the beginning of a series of burns in human volunteers the authors were consciously aware of the undesirability of encountering untoward complications, particularly as represented by uncontrolled infection which might require such treatment as would interfere with the usual medical student routine. Further, the cosmetic end result of these lesions was advertised to the subjects as minimal scar formation. Consequently, we were admittedly overzealous at first in our dressing routine, the lesions which were progressing satisfactorily frequently being redressed several times. As more confidence was gained in our control method, and in some of the experimental treatments, dressings became fewer, and in many cases the original dressing was left until healing was complete. It was soon noted that this had an appreciable

effect in cutting down the healing time. The following figures represent some of the rather striking differences encountered (Table VIII)

TABLE VIII  
RELATION OF NUMBER OF DRESSINGS TO HEALING TIME  
IN 38 LESIONS TREATED WITH SULFAPILM

Number of Dressings	Average Healing Time
5	13 8 days
3	12 1 days
2	9 3 days
1	7 6 days

In the relatively few cases treated with boric ointment the same observation was made, namely, the fewer the dressings the quicker was the healing time. We feel that the reasons are twofold. First, that removing any dressing, even where there is no obvious adherence to the burned area, undoubtedly disturbs and probably removes some of the extremely friable new epithelium. This occurs because the dressing tends to become incorporated in the lesion. Second, the factor of increased contamination which is cumulative with each dressing change may also interfere with the healing process.

*Bacteriologic Findings*—As was stated, routine cultures were taken at the time of débridement and treatment. In approximately 50 per cent of the cases these cultures were positive, despite the fact as has been stated that iodine and alcohol preparation of the selected burn sites was used. In the remainder of cases cultures were negative. By far the more common contaminant was *Staphylococcus albus*. Infrequently *B. subtilis*, micrococcus tetragenes, diphtheroid bacillus and gamma streptococcus (indifferent) were cultured. Important, however, is the fact that no difference was encountered in the healing of lesions primarily contaminated when compared as a group with the lesions which had negative cultures originally. Subsequent infection, when encountered, appeared alike in both originally contaminated and originally sterile areas. Gross infection occurred rarely in this series, but was most common when the escharotics were applied.

*Sulfonamide Sensitization*—Much has been written of late concerning development of systemic sensitivity from the local use of sulfonamides. In the present series this phenomenon occurred only once during active treatment. This was in one of the females who, as was stated, suffered a relatively deeper burn than the males, presumably due to the difference in skin thickness. One of her lesions was treated with the sulfonamide-impregnated film and on the ninth day, at which time the healing was nearly complete, she complained of itching and burning at the burn site. Examination revealed a papular rash, with vesiculation, weeping, and localized edema of the area. Not only was the burn itself involved but also the surrounding skin. This rash disappeared on treatment with bland ointments, and patch tests performed at this time on the anterior aspect of the forearm revealed apparent sensitivity to the sulfonamide-impregnated film, but none to a film of similar

base containing no sulfonamides. Passive transfer tests were uniformly negative. Retesting by the patch method both on the site of the healed burn and on the forearm was negative for further evidence of sensitization. Because of this case, however, 25 of the areas treated with the sulfonamide film were tested by reapplication of the film to the burn site at weekly intervals following healing. In six cases a rash occurred at the burn site on the first test (Fig 9). When retested a week later, three were still positive but none was positive at the end of five weeks. In none of the six subjects was there evidence of sensitivity except at the burned areas. This pseudosensitization is mentioned only because of its academic interest, since it is unlikely that an accidental burn should occur in the same area within a short time in a single individual.



FIG 9.—Sensitivity reaction appearing as a maculopapular rash surrounding a sulfonamide film treated lesion one week after complete healing.

*Rôle of Sulfonamide.*—As we review this series of experimental burns we find several indications that the use of sulfonamides either locally or systemically may exert a definitely beneficial influence. Thus, when a sulfonamide-impregnated film was employed the burns healed in the shortest time on the whole, although positive cultures were obtained on numerous occasions. Signs of inflammation such as heat, redness and swelling, however, were quite uniformly lacking. Again, in the series in which boric ointment was used locally with sulfadiazine by mouth four out of five cultures were positive and the healing time was slightly more prolonged, but again no gross infection

or inflammation developed. When boric ointment alone was used the healing time was definitely prolonged and clinical signs of infection were in evidence.

It would seem, therefore, that the bacteriostatic effect of the sulfonamides is accompanied by shorter healing time, and that complete elimination of infection as evidenced by persistently negative cultures is not necessary for prompt epithelization of deep second degree burns.

Another point in local burn therapy which has been raised lately is whether or not a lesion should be débrided prior to the onset of definitive therapy. To answer this question, five lesions were purposely left with vesicles intact and the sulfonamide film placed over these. The contralateral areas were débrided as usual and treated with the same agent. All lesions were healed in seven days and the comparison of the new epithelium of the two sides showed little difference. In three instances the blister was still imperforate and the fluid had been *reabsorbed* while the lesion healed.

#### SUMMARY AND CONCLUSIONS

A controlled series of 82 second degree burns in human volunteers has been studied and the efficacy of 12 different local treatments has been evaluated.

The best results as measured by rapidity of healing, absence of symptoms and freedom from all complications were encountered in the group treated with a sulfonamide-impregnated plastic film.

The next best, and very nearly as efficacious method, was local treatment with a bland ointment combined with sulfonamides administered by mouth. However, certain qualitative differences were noted between the healing processes of lesions treated with film and those in which boric ointment was used.

The value of the use of the sulfonamides either locally or systemically was clearly demonstrated in the control of infection and the evidence of sensitivity, resulting from their local application, was minimal and of no practical significance.

The importance of restricting the frequency of dressings was confirmed, as there was a direct relationship between the rate of healing and the number of times the dressings were removed.

Under the conditions of this experimental series the lesions which were not débrided healed as well and as rapidly as those from which all nonviable tissues were carefully removed.

Our experience in this series of experimental burns gives additional evidence for the abandonment of any type of treatment with escharotic agents.

Finally, it is suggested that so-called second degree burns should be carefully described as to their depth to facilitate greater accuracy in comparing results obtained in series reported in the literature.

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# TANNIC ACID AND THE TREATMENT OF BURNS AN OBSEQUI\*

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TWENTY YEARS AGO, on May 5, 1924, seven patients who had been burned in an illuminating gas explosion were admitted to the Henry Ford Hospital. These men became the first of a category of treated cases which, in all probability, numbers hundreds of thousands at the present time. Tannic acid was applied to their burns. All survived, and their case histories along with 18 others were included in E. C. Davidson's<sup>1</sup> published paper on the method which appeared in August, 1925. It is hoped that this communication from a group working in the same institution will result in the abandonment of the treatment of burns by this and related methods. This unqualified recommendation is prompted by comparatively recent clinical experience and animal experiments by us and others. Under certain circumstances, the use of tannic acid produces a severe if not a fatal lesion in the liver, and carefully controlled experiments have shown that it is moderately inhibitory to the healing of wounds.

In April, 1940, two of us<sup>2</sup> published a paper entitled "Problems in the Treatment of Burns. Liver Necrosis as a Lethal Factor." It was pointed out that in five consecutive autopsies, there was striking degeneration of the liver. All of the cases had been treated with tannic acid jelly. However, since the lesion had also been seen in at least one case treated by the widely used spray method,<sup>3</sup> the rôle of tannic acid was not immediately appreciated. Several authors called attention to the liver lesion, but did not incriminate tannic acid<sup>4, 5, 6, 7, 8</sup>. Notable among these were Wilson, and his associates, of Edinburgh, who were distressed with the fact that there were deaths from "burn toxemia" in children with small areas involved.

At the Clinical Congress of the American College of Surgeons at Chicago, in October, 1940, Donald B. Wells, of Hartford, took part in a panel discussion of burns, and showed photomicrographs of livers from experimental animals into which tannic acid had been injected subcutaneously. To our knowledge, this was the first public accusation of the tanning method. The article by Wells, and his associates,<sup>9</sup> containing reports of six clinical cases, and the animal experiments appeared in April, 1942. In March, 1942, one of us<sup>10</sup> led a panel discussion on burns at a War Session of the American

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\* Part of the work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Development and the Henry Ford Hospital.

Read before the American Surgical Association, May 3-4, 1944, Chicago, Ill



College of Surgeons, and called attention to the probable relationship between the liver lesion and tannic acid

In February, 1942, a project for the study of burns at the Henry Ford Hospital was approved by the Committee on Medical Research. At the request of the Subcommittee on Surgical Infections, alternate cases were treated by two currently accepted methods, namely, the tanning and vaseline-pressure methods. Extensive studies were carried out on these patients, but only the observations regarding the liver are presented here. Four illustrative cases



FIG 1—Case 1 Eschar from tannic acid jelly has formed

will be reviewed. Two of these were tanned cases and two will be called controls, *i e*, they were treated with the presumably inert vaseline dressing

#### ILLUSTRATIVE CASE REPORTS

Case 1—D L, white, female, age six. She was admitted on March 17, 1942, having sustained severe burns when her clothing caught fire while she was playing with matches. She was found to have deep burns of the face, abdomen and upper extremities (Fig 1). It was estimated that 36 per cent of the body surface was involved (Fig 2). All blisters were removed and tannic acid jelly was applied. Plasma infusions (800 cc) were given during the first 24 hours. A satisfactory correction of the hemoconcentration was obtained (Fig 3). Nevertheless, the clinical course of the patient was not good. There was persistent vomiting on the second day. The vomitus was of the appearance of coffee grounds on several occasions. Bleeding from cracks in the tannic acid eschar was noted, and this observation was in agreement with the laboratory finding of a plasma prothrombin level of zero. Oxygen, whole blood transfusion and adrenal cortex were given. She became comatose, the urinary output became *nil*, and she expired on March 24. All liver function tests showed that profound hepatic

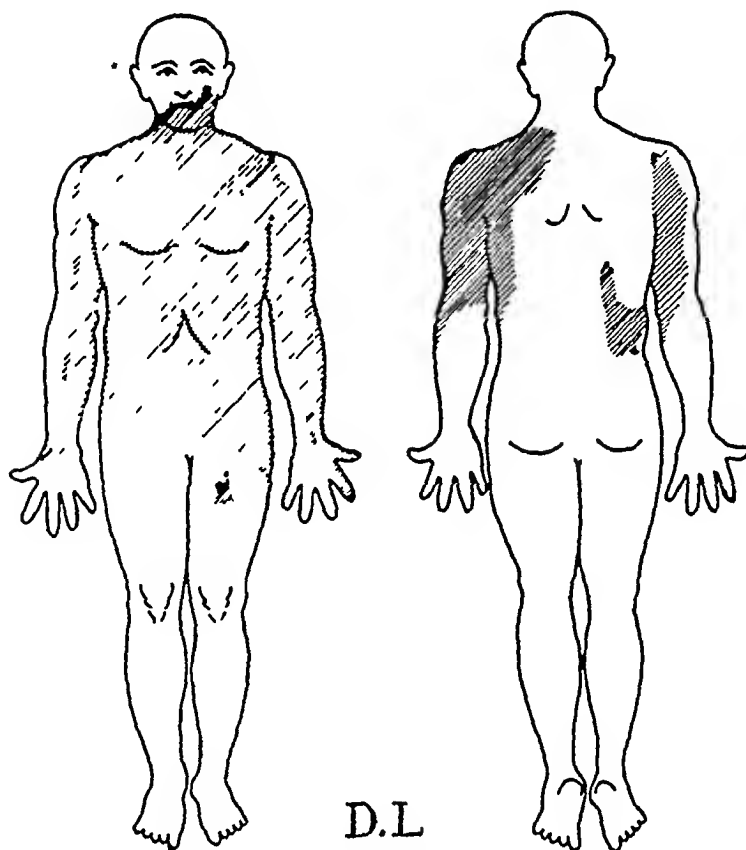


FIG 2—Diagram of all burned areas in Case 1

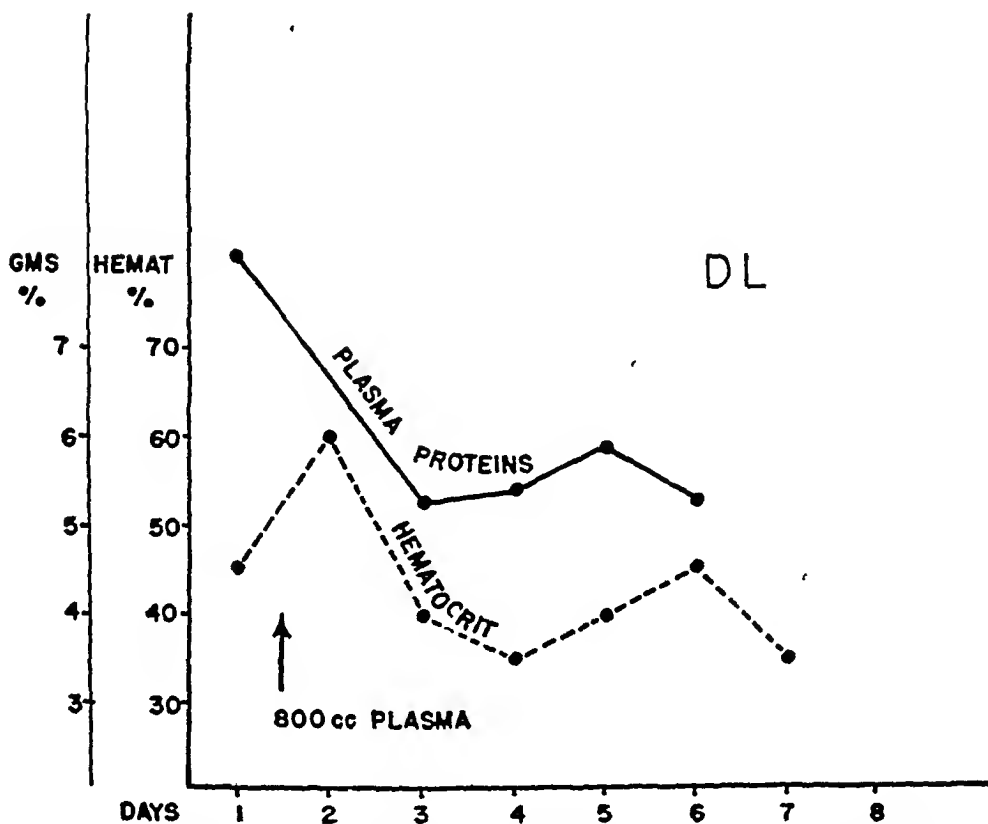


FIG 3—Chart of hematocrit and plasma protein values in Case 1. The correction of hemoconcentration was not accompanied by clinical improvement.

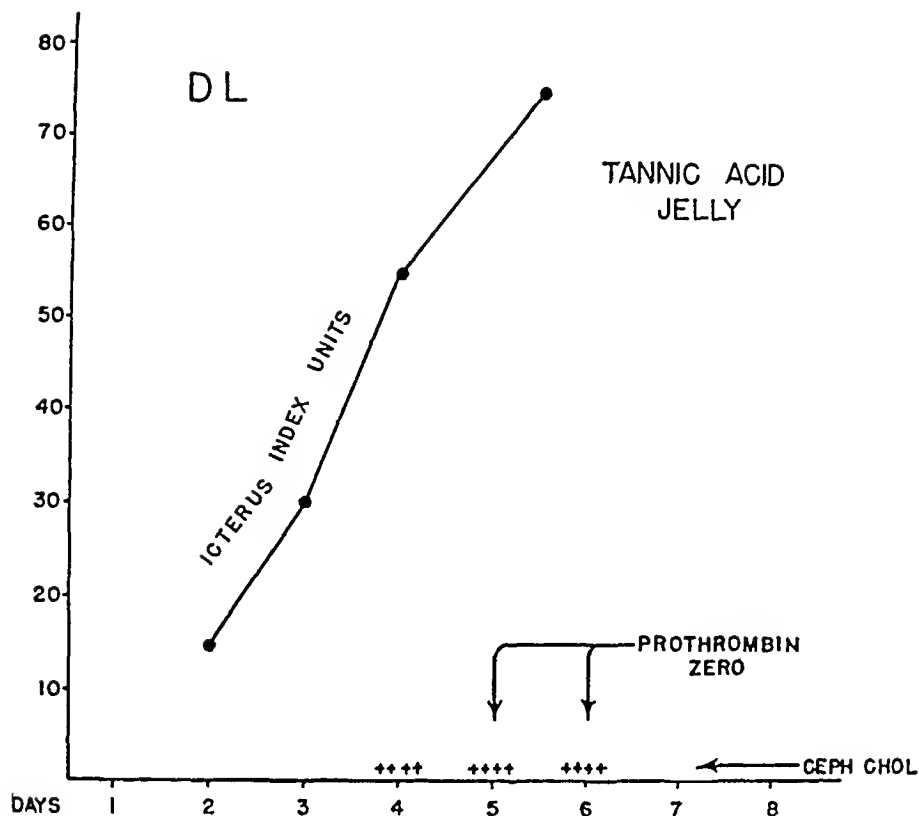


FIG 4—Chart of liver function studies in Case 1

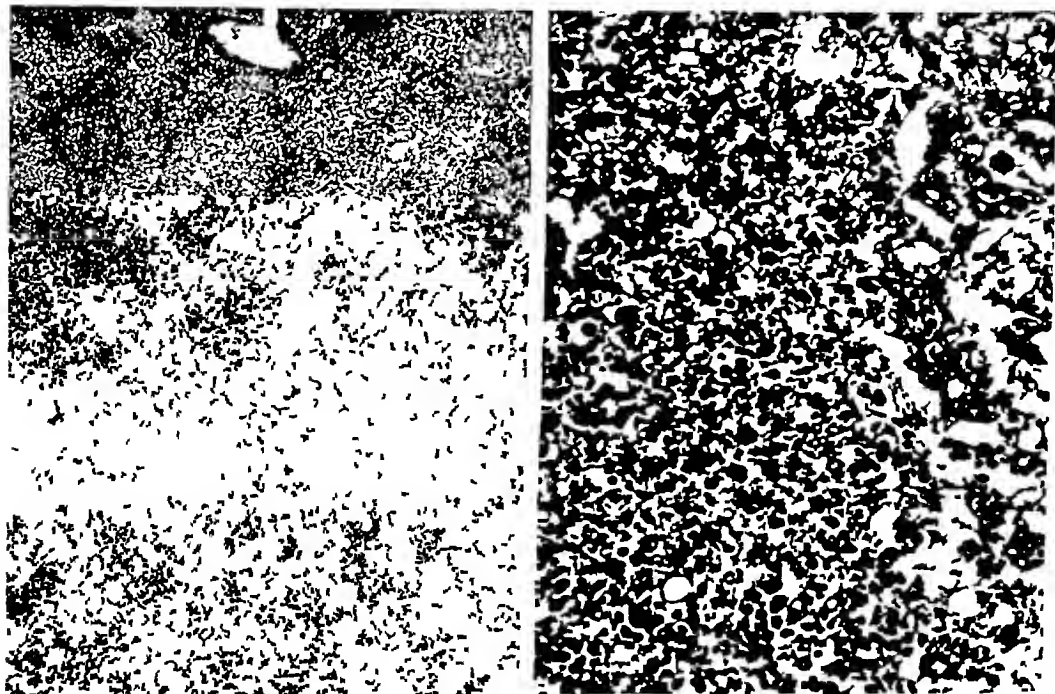


FIG 5—Low and high power photomicrographs of liver tissue, Case 1

damage had occurred (Fig 4) Autopsy was performed The chief finding was the microscopic appearance of the liver (Fig 5) The tissue could hardly be identified as liver tissue, so great was the necrosis

Case 2—M A, white, female, age two On May 5, 1942, her clothing caught fire and she was severely burned She arrived at the Henry Ford Hospital three hours



FIG 6—Case 2 Appearance at time of first dressing (vaselined gauze, with pressure)

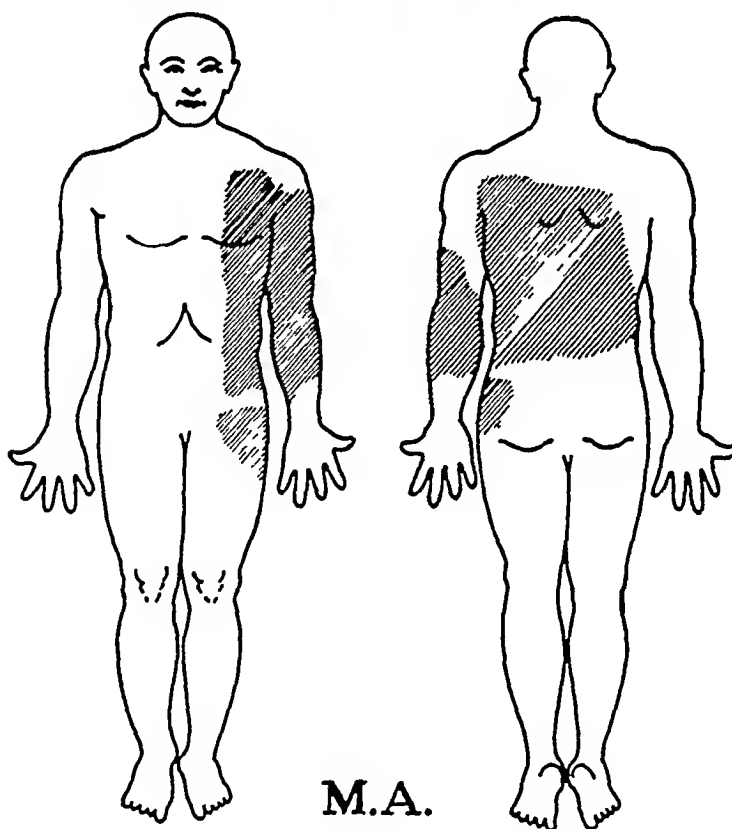


FIG 7—Diagram of burns in Case 2

later Deep burns of the back, left arm and buttock were present (Figs 6 and 7) The blisters were removed, and cleansing was carried out with white soap and water Fine-mesh vaselined gauze was applied under pressure with machinists' waste and

elastic bandages These dressings were not disturbed for two weeks Although there was some fever, at no time did the girl look dangerously ill Liver function tests showed essentially normal values (Fig 8) Three skin grafting operations were necessary to cover the areas of third degree burn, the first procedure being on May 26 She was discharged on June 21 in excellent condition

Case 3—E S, white, male, age 16 On April 21, 1942, he was working in a gasoline station and his oil-soaked trousers became ignited There were second degree burns of the lower extremities, estimated as 22 per cent of the body surface (Fig 9) Blisters were removed and tannic acid jelly was applied within an hour of the injury He received 900 cc of plasma Nausea, vomiting and extreme lethargy developed on the third day and persisted for a week Clinical jaundice appeared on the third day

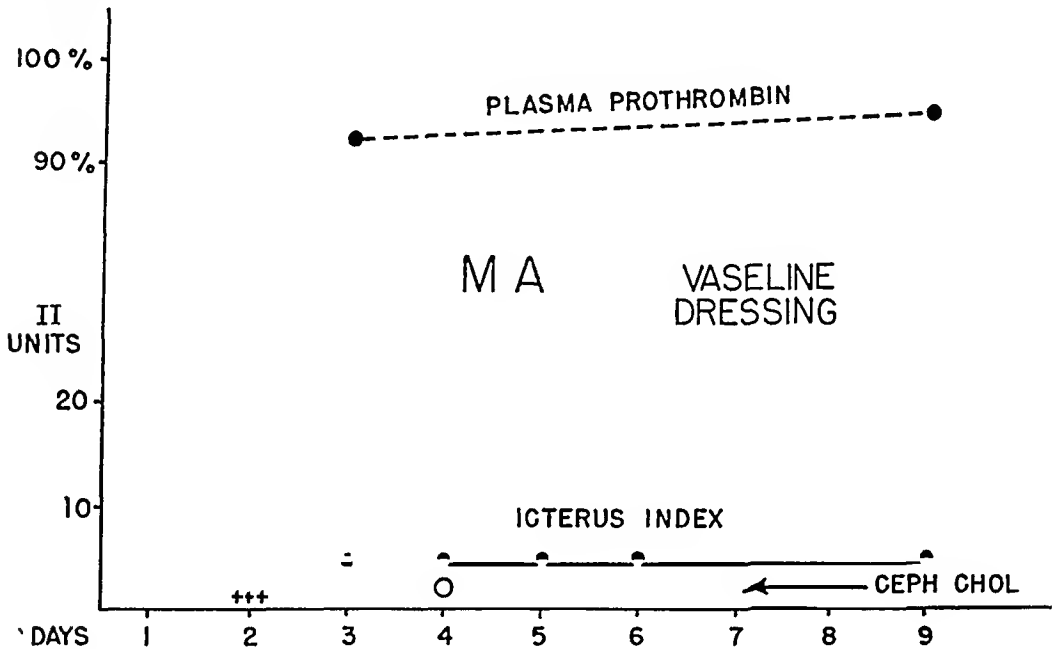


FIG 8—Chart of liver function studies in Case 2

Liver function tests showed marked disturbance of hepatic function (Fig 10) Infection developed beneath the eschars on both legs Healing was complete on May 29

Case 4—C L, white, female, age 28 She was burned in a gas explosion on August 18, 1942, and was admitted to the hospital an hour later, with burns of 31 per cent of the body surface (Fig 11) She was treated with vaselined gauze and pressure dressings She received 2400 cc of plasma The dressings were changed on the eleventh day, and most of the burned areas were healed The liver function studies did not deviate from the normal except that the cephalin-cholesterol test was slightly positive on the third and fifth days (Fig 12)

As far as we know, there are no substantiated cases of liver damage of the grade described in Cases 1 and 3 in patients who have not had their burns treated with tannic acid Others<sup>11</sup> have gone over their pathologic material and have found that the hepatic lesion was present only in the tanned cases The lesion has been reproduced in experimental animals by a number of investigators<sup>12, 13, 14, 15</sup>

In addition to the toxic effect just considered, there is an unfavorable local effect of the tanning method Wound healing is considerably delayed

and border-line second degree burns may be converted to third degree. In 1936, Taylor<sup>16</sup> issued a timely word of caution in an article entitled "The Misuse of Tannic Acid." He pointed out that the "fixing" of tissues, as with tannic acid, meant cell death, and that there was danger of live cells being thus "fixed."

The Padgett dermatome has made possible a convincing type of wound healing experiment. It is possible to obtain two wounds of similar size and depth, one serving as the treated and the other as the control wound. Experiments of this kind, using tannic acid, have been carried out by Cannon and Cope,<sup>17</sup> in Boston, and Hirshfeld, Piling and Maun, in Detroit.<sup>18</sup> Tanning has invariably produced a delay in the healing of these dermatome-donor sites. The latter investigators took biopsies of tanned tissue at various intervals and demonstrated that the depth of the injury can be increased considerably by the use of escharotics.

Brush, Lam and Ponka<sup>19</sup> found that both the 5 per cent aqueous solution of tannic acid and the jelly caused delay in the healing of experimental cutaneous wounds in the guinea-pig (Fig 13).

If tannic acid is toxic to the liver and does local damage, why was it used for 20 years, and why was it adopted so enthusiastically almost all over the world? What about the much publicized mortality rate reductions? We fear that the largest factor was "wishful thinking." The management of a badly burned patient was (and still is) such an onerous task that any method with possibilities would have been received with open arms. Scientific evaluation of a burn remedy is notoriously difficult and unreliable. It has taken 20 years to evaluate tannic acid. A review of the early articles on this method of treatment shows that many of the reported series were remarkably small. Many times, the mortality was high, but various alibis were given. One paper<sup>20</sup> reported that the death rate had been cut in half by the new treatment, but it is noted that the primary mortality rate was unreasonably high (40 per cent). As a matter of fact, the mortality rate at the Henry Ford Hospital was not improved with the adoption of tanning, a fact which was indicated by statistics published in 1935<sup>21</sup> and 1940.<sup>2</sup> These figures and the most recent ones may be seen in Table I.



FIG 9—Case 3. Burned areas. Healing is almost complete. Tannic acid.

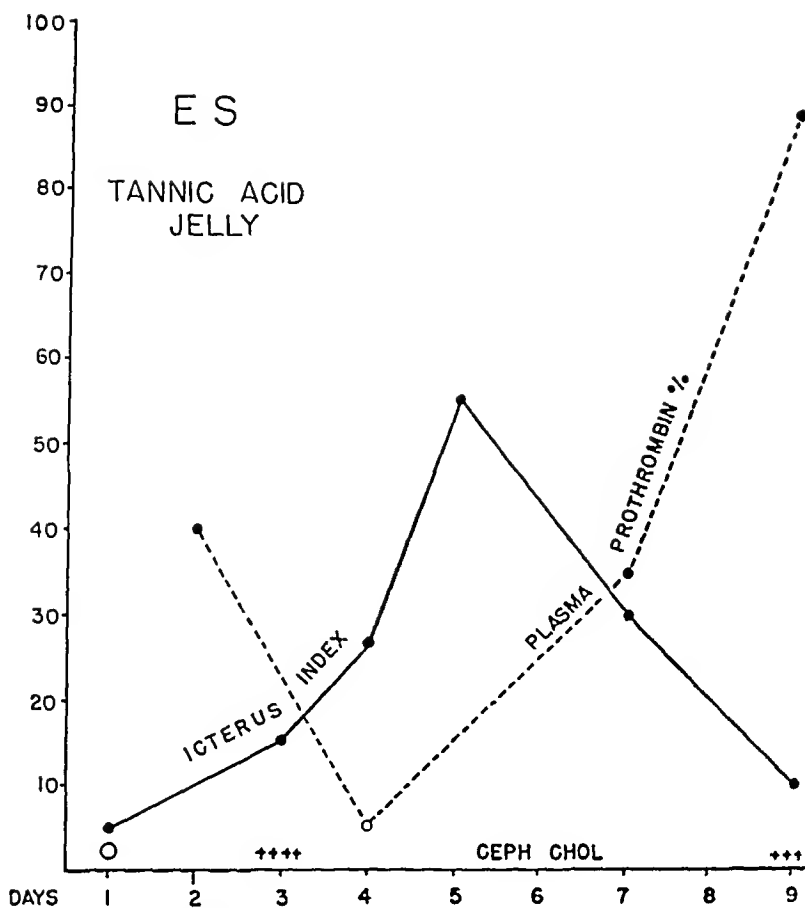


FIG 10—Chart of liver function studies in Case 3

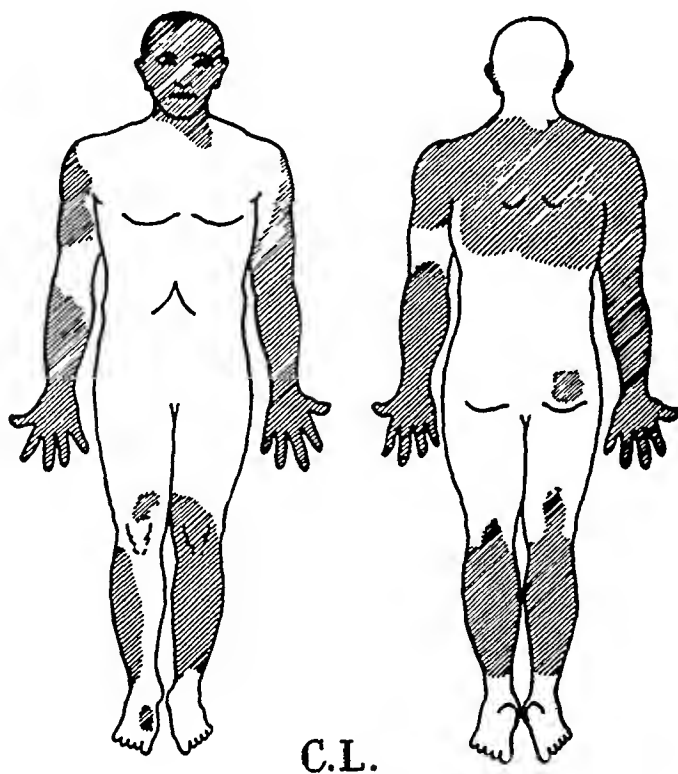


FIG 11—Case 4 Diagram of burns used Vaseline dressings were

# TANNIC ACID TREATMENT OF BURNS

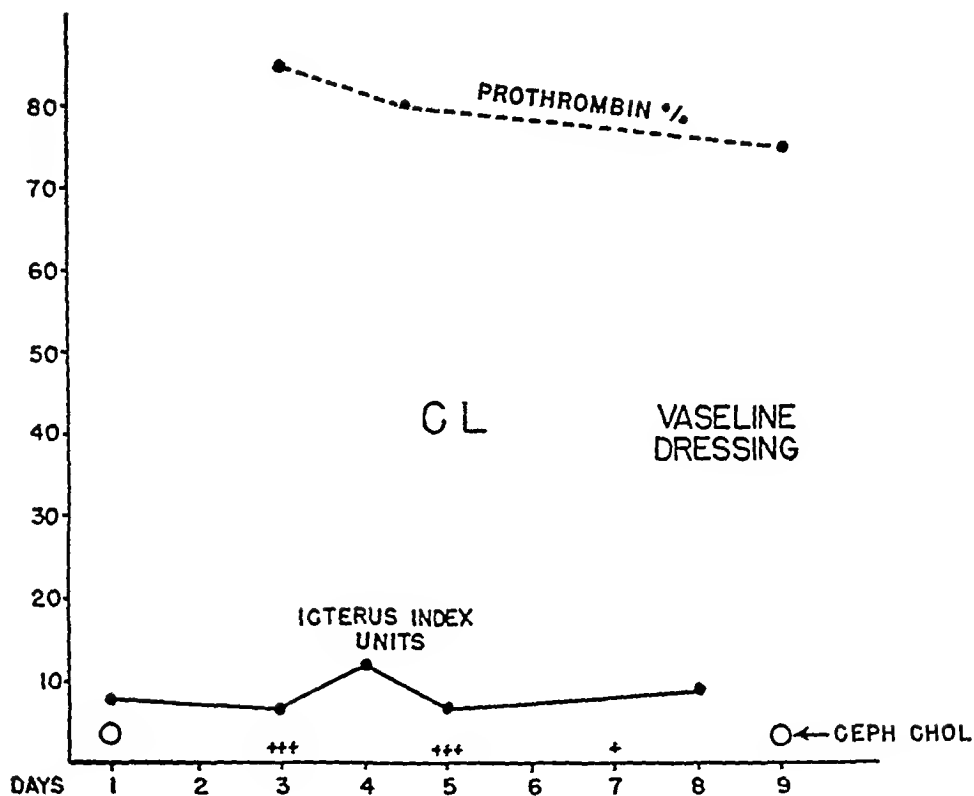


FIG 12—Chart of liver function studies in Case 4



FIG 13—Wound healing experiment showing inhibiting effect of tannic acid jelly. Both wounds were the same size ten days before. Control wound (arrow) is healed.



TABLE I  
BURN MORTALITY RATE AT HENRY FORD HOSPITAL

Date	Method	Cases	Deaths	Mortality Rate
1916-24	Various	118	11	9.3%
1925-36	Tannic acid	358	42	11.7%
1936-40	Tannic acid jelly	125	22	17.6%
1942-44	Vaseline	80	2	2.5%

It is probable that in many hospitals there was an actual decrease in the mortality rate during the "tannic acid era." After Davidson's paper, there was infinitely greater interest in burns. All aspects of treatment became better. In the more recent years, severe cases were given large amounts of

FIG 14



FIG 15

FIG 14—Case 5 Showing well formed tannic acid eschar  
FIG 15—Case 5 Four weeks after injury Subcutaneous fat is visible everywhere on lower extremities  
The depth of tissue necrosis prevented tannic acid absorption

plasma in addition to their tanning treatment. It is obviously improper to assume that the recovery of such a case was due to the local treatment.

Some explanations are at hand regarding the inconsistency of the appearance of the specific liver lesion. The method of application may have increased the rate and amount of absorption. It is undoubtedly significant that the cases reported by Wells were treated in a tub bath, and most of our own cases were treated with a jelly, which was relatively slow to dry. Many severely burned patients did not absorb much tannic acid on account of the

extreme depth of their burns. A second degree burn presents the best absorbing surface. The following case is one in which there was probably little or no absorption due to the uniformly great depth of the burn.

**Case 5**—B S, white, male, age 21. Admitted on February 11, 1941, after his oil-soaked clothes caught fire. He had a third degree burn corresponding to the area covered by his trousers. A good eschar was obtained with tannic acid jelly (Fig 14). He was given 2500 cc of plasma. At no time did he show signs of shock or any symptoms of hepatic insufficiency. The icterus index during the first month was not above 10. Tissue injury was extreme, however, as can be seen from a view taken after four weeks, showing all of the eschar removed, and no epithelium visible from the heels to the waistline (Fig 15). This patient expired on the fifty-fifth day, of inanition and sepsis. He became refractory to transfusions of any type, and was not benefited by the heroic gesture of homografting. However, his death was not related to early burn shock or toxemia.

#### SUMMARY

Liver necrosis has been reported in a considerable number of burned patients treated with tannic acid. Nonfatal cases frequently show marked disturbance of liver function in the acute phase of the burn. The liver lesion is easily reproduced experimentally. Wound healing experiments on animals and on human donor sites indicate that tannic acid retards healing considerably.

In writing this "obsequy" for the tannic acid treatment of burns, it is far from our desire to write off the work of the late E C Davidson. He was an indefatigable worker and a keen observer. Had he lived, he might have recognized the shortcomings of his method before the others we have mentioned. It is certain that we would be further along on the burn problem if we had had his help beyond 1933.

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DISCUSSION—DR JONATHAN E RHODS, Philadelphia We are grateful to Doctors McClure, Lam and Romence for their paper, because it will be helpful to surgeons everywhere to know that the tannic acid method has been abandoned by the institution from which it was introduced

One of the perplexing things about the history of the tannic acid method is the tremendous clinical experience which attested its value in reducing burn mortality Nearly every report except that which Doctor McClure made several years ago, mentioned a reduction in mortality of approximately 50 per cent It has been suggested that the improved mortality was due to other changes in treatment, but it seems doubtful if such a large number of good clinical observers would have overlooked this fact had it been true

Even if it should be true that the reduction in mortality was brought about by other factors, it is difficult to believe that the tannic acid method as generally used, actually caused the death of many patients who were not going to die anyway

Those who died with a picture of toxemia generally showed marked changes in liver function, and during the period when tannic acid was widely used the changes in liver function and the histologic changes in the liver of those patients who died were regarded by many people as the cardinal signs of toxemia

At the Pennsylvania Hospital since the tannic acid method has been given up, we have observed that toxic deaths still occur In fact, since the advent of better methods of treating burn shock, a larger proportion of deaths following burns appears to be due to toxemia

Recent studies, carried out under contract with the Office of Scientific Research and Development, indicate that mild changes in liver function still occur in patients treated with vaselined gauze and pressure dressings

In this series of patients you will notice that the cases have been classified according to the rise in the van den Bergh test A number of other liver function tests were carried out, and of the group the van den Bergh seemed to be most representative of the changes observed

Twenty-nine per cent of the patients treated with tannic acid had an elevation of

the serum bilirubin of two milligrams, or more, and all of the extremely high elevations, such as one of 11, one of 13 and one of 16 milligrams per cent, occurred in that group.

Patients treated with other tanning methods, mainly silver nitrate or silver nitrate and methyl rosanilin, had a rise in the bilirubin of over two milligrams in 17 per cent, and those treated by nontanning methods in only seven per cent.

We agree that the evidence against the use of tannic acid is so definite that it should be abandoned. However, it is difficult to escape the conclusion that the method was a useful one during the years following its introduction, that it probably caused very few liver deaths in patients who would not have died anyhow, that it was perhaps the first type of dressing that was not changed during the first ten days, and that it did tend to prevent infection during the early stages when the patient was in his greatest danger from shock and toxemia.

Undoubtedly, one of the reasons which has facilitated the revival of methods similar to methods which tannic acid displaced, is the possibility of controlling invasive infection by the use of sulfonamides.

DR. ALVIN O. WHIPPET, New York. Of the many problems studied by the Subcommittee on Burns of the National Research Council none has been more difficult than the treatment of the extensive third-degree burn. As a result of the newer measures for combating shock and infection, many of these severe burns that formerly died in the first three to five days survive to become problems in chronic infection, hypoproteinemia and nitrogen imbalance, anemia, weight loss and nutrition deficiencies. Removal of the slough and skin grafting of the remaining granulating area of these patients, shorten their hospital stay and minimize their scarring and contractures than any other therapeutic measure.

The hastening of the sequestration and removal of the slough have been under investigation during the past two years by Beard of Duke University, using pepsin and silicic acid, and by Howes, of Columbia University, using hydrochloric acid and pepsin, and many other acids and enzymes. But by these methods, although the slough was liquefied and disappeared quickly, the remaining surface was not a suitable one for the taking of skin grafts.

Doctors Harvey and Conner have made a real and significant contribution in their use of pyruvic as a means of removing whole-thickness slough, leaving a suitable granulating surface for immediate or prompt skin grafting. If the clinical results will be in any way comparable to the experimental burns we have seen in their laboratory a great step forward will be taken in the treatment of whole-thickness burns.

We have found a great difference, however, in the use of pyruvic acid on small areas as compared with extensive areas of slough. In the former it is possible to keep the acid active in a starch base, but in an extensive slough, with considerable exudation and with considerable variation in the thickness of the slough, the maintenance of the optimum pH of 1.0 is difficult and the slough does not separate evenly.

However, in the few patients upon whom we have used this preparation, it is evident that the acid does not damage normal skin, it does not convert second-degree areas into third-degree, it demarcates third-degree areas early, it is painless, and it undoubtedly causes an early separation of slough, leaving a granulating base suitable for early skin grafting.

There are several problems that will have to be studied carefully before the method can be generally recommended. One is the question of what the limit of the area is on which the pyruvic acid is applied before an acidosis is produced. Secondly, is there a danger in removing too extensive a slough, leaving a granulating surface that cannot be promptly skin-grafted without removing an amount of normal skin beyond the donor area limit in amounts that would cause severe shock? Stamp-grafting areas from which slough has been removed at intervals would be necessary in extensively burned patients.

DR CHARLES C LUND, Boston These four papers are very difficult to discuss because they bring up, in one way or another, most of the important problems of burns, and in five minutes I can only select one or two things to consider

Doctor Andrus' experimental burns are very ingenious, a very useful method, and I think Doctor Dingwall's results are very important. To me the most important table was almost the last table that he presented, that is, that the less often you dress a burn, the faster it heals

I have felt that so strongly that recently, at a meeting of doctors under the auspices of an insurance company, with some of the insurance company's officers present, I suggested that maybe the insurance company should take a leaf from the New Deal and find out how many dressings the fussiest doctor would be apt to do for a given burn, and then pay the doctor a flat rate for not doing those dressings

The difference between boric ointment and the sulfa film was certainly significant and interesting. I have become such a therapeutic nihilist on the subject of chemical applications to the surface of burns, that, as some people know, we have given up any application now except dry gauze, counting on rest, pressure with or without plaster, as creating as good conditions as we know of for the healing of a burn, and allowing those dressings to remain up to three and even four weeks

The conditions here, with ambulatory patients, certainly do not give the conditions of rest that you get in a suitable Allen-Koch type of pressure dressing

I was a little surprised that there was as much evidence of infection under the boric ointment treatment, either with or without sulfa drugs, as there was in this series, and I can explain it only on the basis that if these men had been in bed during the treatment, there might have been somewhat less infection

However, the conclusions of this paper and the data are quite important, and they are another expression of the fact that we must avoid employing any treatment that delays the healing of a burn. We cannot actually stimulate the healing of a burn. The healing of a burn is done by nature, if we can create the right conditions, nature can heal it very rapidly

Just a word about Doctor Moyer's paper. In the first place, I want to ask him a question. How much hemoglobinemia was seen in these dogs with their extensive deep burns? From the experiments in much smaller burns of dogs and calves that C K Drinker, of Boston, has carried on, I would have expected there would be a great amount of blood destruction from the thermal injury of the blood in and under the skin in these dogs

This paper has given me a great deal to think about, and I believe it is as important or more important than any paper I know of on the chemical aspects of burns in the last two or three years

We are finding, by chemical tests on human patients, that there are very significant differences in the chemical blood changes associated with deep extensive burns from those changes of the same items in the widespread second-degree burns, and the problem of treating the extensive third-degree burns is certainly, according to our data in our hands, a much more complicated one than just trying to keep the hematocrit at a reasonable level by pouring in plasma

We have not anything published on it yet, but we ourselves are getting very suspicious of possible harm from the citrate in the ordinary plasma when we are using three or four liters of plasma

We are also very doubtful about lactate, as Doctor Taylor of our group will present shortly. The blood lactic acid goes up as much as ten times in some burns without the administration of any lactate. The sodium bicarbonate in the blood, if the burn is very severe, may go down, and it may go down to a significant extent

Therefore, it is quite logical that if you are to treat to prevent or treat acidosis,

you had better do it by bicarbonate rather than by lactate. We cannot put that out as final, but it is one of the things we are working on.

I was delighted at Doctor Connor's and Doctor Harvey's method of removing slough, and I am glad to hear that at least it is not dangerous to apply to humans.

It looks to me like the kind of thing that many of us would like to use in cases very shortly.

DR ALFRED BLALOCK, Baltimore, Md. I have never been an advocate of the tannic acid method for treating burns, but I doubt if the method should be completely abandoned. It might be the expedient method when numerous burns have to be treated on a ship. I would certainly doubt the wisdom of placing on large pressure dressings under such circumstances if there is a possibility that the ship will have to be abandoned.

My purpose, however, is to discuss the paper by Doctor Moyer, and his associates. I agree with Doctor Lund that this is an excellent study. A great deal of attention has been focused recently on the treatment of burns and other injuries by the use of salt solution. Much of this interest is due to the work of Rosenthal, of the Public Health Service, on the treatment of burns in rats and in mice. He finds that all sodium salts are equally effective and that the administration of salt solution by mouth or by vein is as effective as the intravenous use of blood serum or blood plasma. One criticism which has been levelled at these experiments is that the treatment is carried out almost immediately after the infliction of the burn. A second criticism is that tremendous quantities of fluid equal to 8 to 15 per cent of the body weight are given. Even if his observations apply in man, a real difficulty would be encountered by the armed forces under many circumstances in having available such large quantities of fluid.

Doctor Prinzmetal has also carried out similar experiments on rats and mice and he finds, also, that isotonic saline is as effective as plasma.

Doctor Haist, of Canada, on the other hand, has been studying a somewhat similar type of injury, namely, tourniquet shock. Hemoconcentration occurs under these circumstances just as it does in burns. He waits several hours in these studies before carrying out therapy and finds that salt solution is far inferior to plasma therapy. Dr C. N. H. Long, of Yale, has produced shock by the slow withdrawal of blood, and, here, it is found that plasma is far superior to salt solution.

Doctor Moyer, and his associates, as you have heard, have come to the conclusion that the administration of defibrinated blood by vein and of salt solution by other routes constitutes the ideal treatment for experimental burns in dogs. The method which they have used in causing burns consists of immersion for 30 seconds. This type of "cooking burn" is not encountered frequently in man.

The emphasis which some of these investigators have placed on the giving of fluids by routes other than the intravenous one raises the question as to whether fluids will be retained and absorbed when given by mouth and whether they will be absorbed when given subcutaneously or by rectum.

Patients in shock are very apt to vomit when given large quantities of fluid by mouth. The question arises as to whether the vomiting is due to impaired circulation or whether it is due to morphine which may be given to control pain. It is stated in a recent note from Major Beecher in North Africa that the vomiting is frequently due to the morphine. I am inclined to think, however, that many patients in shock will vomit even though no morphine is given. Certainly it is true that patients in severe shock absorb fluid from the tissue spaces very poorly. It is agreed that fluids should be given by mouth if they are retained.

Doctor Fox has reported good results in the treatment of burns in man by the use of sodium lactate by mouth. The experience of Dr E. I. Evans, of Richmond, in this regard has not been so encouraging. Doctor Evans is here and I hope that he will comment upon this point.

It would seem to be a fundamental principle in fluid replacement that one should re-

place the loss as nearly as possible by fluid of the same composition. It is an incontrovertible fact that large quantities of plasma containing protein are lost at or near the site of severe burns. It would seem that the burden of proof is on the person who says that the treatment of burns should not include the administration of blood plasma. If fluids containing sodium salts are retained and absorbed when given by mouth, it would appear that this makes for an additional important therapeutic aid. I am confident, however, that the use of such sodium salts to the exclusion of plasma will result in a great deal of harm. We should continue to use plasma in the treatment of burns unless it is shown by studies on man that other methods are equally effective.

DR EVERETT EVANS (Dept of Surgery, Medical College of Virginia, Richmond, Va.) At Doctor Blalock's invitation I would like to discuss these papers very briefly, because I think we have had a great amount of clinical experience with severe burns.

Our service has had now close to 200 hospitalized burns. First, we agree with almost everything that Doctor McClure has said about tannic acid. Fortunately for us we stopped the use of tannic acid when we took over the treatment of burns as a research project. In the present series, the only patient treated with tannic acid (by error), a child, died on the seventh day with a history that reads almost exactly as the one presented by Doctor McClure.

We would take exception to one statement in the abstract, that is, "that there need be no concern about the liver in a burned patient if tannic acid is not used."

We have now four extensive burns (not treated by tannic acid) that have come to autopsy. By "extensive" I mean 60 to 85 per cent of the body surface burned, each of these has shown a moderate to very severe liver damage on histologic section. It may be that we are dealing here with liver damage in patients in acute starvation. They lived for from five to seven days.

Our experience with sodium lactate, following Doctor Fox's contribution, has been very disappointing. There were three deaths, consecutively, in patients treated with sodium lactate. It did not control the shock, unfortunately, in two cases we got in only a very small amount of lactate because the children died very shortly after the therapy was started.

In the one case treated very heroically with sodium lactate, blood volume studies (and I may say incidentally we do blood volume studies by the dye technic on most patients) indicated that sodium lactate had no effect whatsoever in increasing the plasma volume of this severely burned patient. In fact, it stayed about 17 cc per kilogram, or 30 per cent of normal, until plasma was given.

I think Doctor Whipple would be interested in our recent experience with the rapid removal of a third-degree burn slough which, I am sorry to say again, unfortunately ended in death. At the suggestion of the Burn Committee we had the Duke University group come and try their solution on a burned child 8 years of age, with a 60 per cent surface burn, third-degree. It was elected to treat only one-half of the burned surface at one time. I must say these men that Doctor Beard sent up were extremely careful in everything they did.

We did blood volume studies, gave transfusions and large amounts of fluid. The child, unfortunately, died about eight hours after treatment was started, in what seemed to me to be severe shock.

So it seems to us who have had some experience with very widespread third-degree burns, that it is probably far better to remove slough slowly in an extensive burn, better to pay the price of having some scarring, than to lose a life with the rapid removal of third-degree slough.

DR ROY D McCLURE (closing) We did not bury this treatment too deeply. I was hoping Colonel Robert Harris might discuss this subject. I know there are many advocates still of the tannic acid treatment, and a lot of people do believe in a resurrection. We do not at the moment.

We have searched for liver sections from patients dying as a result of burns, which might show a central necrosis similar to that produced by tannic acid. This search has been without success. One of our men has offered a prize for such sections, and I am sure Doctor Lam will be especially anxious to see Doctor Evans' cases.

One thing that has held up tremendously the advance in the study of the cause of death after severe burns, is the fact that these cases are always cases for the coroner. Too often the coroners have reviewed the corpse and refused an autopsy, with the statement that "Anyone can see that *that* patient died from a burn!"

DR J. WALTER VAUGHAN, Richmond, Va. It does seem unnecessary at the moment to show slides showing the extent of an injury, but I should like to show them anyway, if I may.

(Slide No. 1) This shows an incision of the subcutaneous tissue and the marked hemorrhage that occurs adjacent to the skin.

(Slide No. 2) This slide shows a kidney which I shall not comment upon at the moment, but you will see the small bowel adjacent to the kidney, which does show a degree of injury.

(Slide No. 3) This is an interesting slide showing an animal that has been treated with serum and saline, using a knife handle as the index of the degree of edema, and a bit of normal skin and subcutaneous tissue as the white tuft immediately above the injured area, with the blood less than half the amount if edema of this nature occurs.

(Slide No. 4) This slide shows a heart with marked subepicardial hemorrhages along the anterior descending coronary artery.

(Slide No. 5) This is an interesting slide showing a lung and an interesting reaction along the proud pleura, with marked hemorrhages along the intercostal vessels.

DR CARL A. MOYER (closing) In answer to Doctor Lund's question, the slide that you saw showed dogs that were treated with saline and serum. That degree of hemorrhage is almost invariably present when this form of therapy is employed. The amount of hemorrhage present in animals treated with blood I V and water by mouth was about one-third of that seen in animals treated with serum. The hemoglobinemias amounted to as much as 1.6 Gm per 100 cc in the period immediately following the injury, it usually decreased sharply within one hour. The largest amount of hemoglobin collected in the urine in 24 hours was 130 Gm. After the first day there was no appreciable hemoglobinuria.

As I said before, the tendency to generalized bleeding is present when serum and saline, and red blood cells and saline, are injected intravenously after the scald. If blood is given with salt, the generalized bleeding does not occur.

In the animals that were successfully treated (blood I V and saline bicarbonate orally) the treatment was begun with the administration of the salt solution one and one-half hours after the injury. The addition of blood was withheld for three hours. At that time a majority of the animals showed distinct signs of shock. It was interesting to notice that the movement of the salt solution out of the stomach within the first hour and a half was usually very small, and many of the animals vomited before the blood was given intravenously.

After the blood was given intravenously the rate of the stomach emptying approached 30 cc per kilo per hour, which is within the normal range of movement of fluid out of the stomach in normal dogs.

We have, likewise, seen this phenomena in man, that is, in the absence of adequate blood replacement vomiting is common, and fluids given orally are not retained. After adequate replacement of the blood has taken place, they do not have as much trouble keeping the fluids down as they had before.

The composition of the salt solution is also pertinent to vomiting. The observations



of Underhill suggest it. He noted that should vomiting occur in burned men who had been given a large amount of isotonic saline that the administration of 5 to 10 Gm of sodium bicarbonate would frequently stop it.

We hold no brief that plasma is not of value. However, the only thing that we have to say is that we are incapable of handling serum safely in dogs injured as severely as these and that serum (or plasma) is not as innocuous a substance as we have been led to believe.

There is no question whatever in my mind that should we reduce the degree of thermal trauma we could effect recovery with the combined use of serum and sodium chloride, sodium bicarbonate solution, as well as with blood and interstitial salt solutions, and if we would reduce the injury more we could effect recovery with salt solutions alone.

DR. FREDERICK A. COLLIER (closing). We have not had the opportunity to try this on human beings. It is our misfortune, and perhaps the fortune of the patients, that in our clinic we see very few burns. However, we do feel that the principles which have been discussed this morning, which have been developed in the experimental animal, have application to other clinical syndromes as well as those of burns.

I mention it now in the hope that some of our friends who may see these lesions may have an opportunity to try out these things that Doctor Moyer has mentioned. We feel that crushing injuries at times are quite analogous to burns and may be managed in the same way. We have had two cases of acute venous occlusion resulting in hypotensive states, with loss of four liters of fluid of some kind to the site of the lesion by our calculations, which presented this same problem, and which were treated along these lines. We feel that some of the gas gangrene infections may also give use to abnormal states that may well be treated along this line. I exclude, of course, the bacterial aspect of it.

I simply mention these other clinical pictures, in the hope that some of you who may see them will be good enough, within the next year, to try some of this therapy.

DR. SAMUEL HARVEY (closing). In the presentation we did not go into the clinical application of pyruvic acid because the experimental work is still going ahead, and we have not adopted any standard application of it in the clinic.

It is quite certain the pyruvic acid, like succinic acid, has very little likelihood of being toxic from any possible absorption from burns. It is probably destroyed rapidly in the body because it is concerned in the intermediary carbohydrate metabolism normally.

The question of removal of third-degree slough over a large area, and the systemic effect of so doing, is certainly a pertinent one, and it is not desirable that this method should be applied except in relatively small third-degree areas until one has gained adequate experience.

Inasmuch as the clinical application of it has been opened up in this discussion, I think I should ask Doctor Connor to present briefly some material that we have.

However, I should like to say that our reason for not presenting clinical material was that we are not prepared, nor do we desire, to have this method applied until we, as well as certain other selected groups, have had sufficient experience so that all the details of the application of it can be given with the proper safeguards.

DR. GERVAISE J. CONNOR (closing). For emphasis I should like to repeat that this method was standardized in animals, with a view to determining whether or not with it could be satisfied the three objectives we had set up, namely (1) The rapid removal of the slough, (2) without significant injury to living tissue (i.e., the conversion of deep second- into third-degree burns), and (3) the development of a base which would immediately accept a graft.

Obviously, this question is first in importance. The experimental results have shown that these objectives can be satisfied in burns in animals.

This cannot be taken necessarily to mean that in the treatment, since there may well be a different optimum with respect to the manner of application of the method under these conditions. The results shown in the following slides indicate that the problem of removing the slough in burns in patients should be satisfactorily soluble by this method, although further study is necessary to perfect its use under these conditions.

(Slide No 1) This is a patient who was admitted one week after a fire burn of the leg. He had been treated at home, the local treatment including cod-liver oil and various ointments, and came to the hospital only when he had developed a local infection. The wound was treated with a *generous* application of pyruvic acid paste at a  $p_H$  of 1.9. It is pertinent here to emphasize that the paste must be maintained in place, for otherwise one can scarcely expect the slough to separate rapidly.

(Slide No 2) In this patient the slough separated completely within six days after admission in spite of the fact that for the first three days the pyruvic acid paste was not reapplied. The base of the wound was then acceptable for immediate grafting.

(Slide No 3) This slide shows the undamaged strip of unburned skin on the back of the same leg, which area of skin was included under the dressing.

The wound was subsequently grafted after further exposure to the same pyruvic acid paste, there being no evidence of injury to the base of the wound after this additional treatment.

# THE SURGICAL TREATMENT OF CARCINOMA OF THE BODY OF THE PANCREAS\*

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RESECTIONS OF CARCINOMA of the body of the pancreas have been reported on rare occasions since the first solid tumor of this organ was excised in 1882 by Trendelenberg. Up to 1930, Oberling and Guerin<sup>1</sup> were able to collect only 11 instances of successful resections of malignant neoplasms of the body. These included four "epitheliomas" and seven sarcomas. The literature since 1930 contains but few reports of such cases. In Gordon-Taylor's<sup>2</sup> patient, a male, age 54, a large epithelial tumor arising in the midportion of the body was excised in 1927 but not reported until 1934. In 1938, Doberer<sup>3</sup> reported two instances of resection of carcinoma of the body of the pancreas, in one, the tumor arose from the superior border and was about "the size of a prune," in the other the neoplasm was quite large, involved the distal seven centimeters of body and tail, and also necessitated splenectomy. The first patient was well two and one-half years later, the second died on the fifth postoperative day. In the patient cited by Milhet, Dormay and Feyel<sup>4</sup> in 1940 a large carcinoma of the body was resected. There was relief from pain but finally cachexia and death two months later. In the series of six patients with pancreatic cancer reported by Harvey and Oughterson<sup>5</sup> in 1942, their "Case 1" presented a carcinoma of the body that was resected by subtotal pancreatectomy, there was survival for five months, death being due presumably to metastasis. In 1943, Rockey<sup>6</sup> reported an instance of subtotal pancreatectomy for carcinoma extensively invading the organ, the patient died 15 days later of bile peritonitis.

The purpose of this communication is to record a small personal series of patients in whom attempts were made to deal with carcinoma of the body of the pancreas. There were six resections of the body, including the spleen, and two total pancreatectomies, including total duodenectomy and splenectomy.

The technic for resection of the body of the pancreas has been evolved principally as a result of experience in recent years in excision of pancreatic tissue for hyperinsulinism. The steps in the technic of such resections employed in the patients reported here may be summarized as follows (Fig 1)

Anesthesia. Preferably continuous spinal

- 1 High midline, transverse or inverted-T incision
- 2 Approach to the pancreas by transection of the gastrocolic omentum from the level of the head of the pancreas to the gastrosplenic vessels
- 3 Retraction of stomach upward and transverse colon downward

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\* Read before The American Surgical Association, May 3-4, 1944, Chicago, Ill

4 At this point, the body of the pancreas may be excised in one of three ways depending upon the expediency of each situation

a Transection of pancreas at level of the neck, with resection proceeding distally of body and tail, hemostasis being secured by ligation of branches from the splenic vessels

b Division and ligation of gastrosplenic vessels, then transection of neck of pancreas and splenic artery and vein at this level, with excision of body of pancreas and spleen *en masse* proceeding from the neck distally

c Division and ligation of gastrosplenic vessels, then elevation of spleen by grasping in right hand, this brings the tail and body of pancreas forward together with splenic artery and vein. Transection of neck of pancreas and splenic vessels at level of superior mesenteric vessels, with excision of body of pancreas and spleen *en masse*

5 Interrupted interlocking silk mattress sutures are placed about 0.5 cm proximal to the cut edge of the remaining neck of pancreas. The transected main pancreatic duct, if apparent, is grasped with a hemostat and ligated separately

6 The transverse mesocolon is repaired except in the region below the pylorus. Here, one or two soft rubber drains are inserted to the site of pancreatic transection

7 Closure of the abdominal wound

In some instances of redundant stomach the gastrohepatic omentum may be transected, the stomach retracted downward and the body of the pancreas excised over the lesser curvature of the stomach

Total duodenopancreatectomy and splenectomy for practically complete replacement of the pancreas by carcinoma was performed in two patients as follows

1 In each instance the pancreas was exposed *via* the gastrocolic route

2 The gastrosplenic vessels were divided 3 The spleen was grasped with

the right hand and elevated to mobilize the body of the pancreas 4 The

splenic vessels were divided about three centimeters distal to the origin of the

portal vein 5 The peritoneum along the convex border of the duodenum was

incised to mobilize the head of the pancreas and duodenum 6 The pylorus

was transected several centimeters proximal to the pyloric sphincter, and

upper segment of stomach closed 7 The common bile duct was transected

below the level of the superior border of first portion of duodenum 8 The

head of the pancreas and duodenum were completely mobilized and lifted

away from the superior mesenteric vessels, the uncinate process of the pancreas

and terminal portions of duodenum brought out to the right from beneath these

vessels after transection of the ligament of Treitz 9 Transection of jejunum

just distal to ligament of Treitz and closure of distal segment 10 Removal

of entire pancreas and duodenum with attached lower pylorus and spleen

11 Gastro-enterostomy (Billroth II) 12 Choledochojejunostomy using

loop of jejunum about 15 cm distal to above anastomosis, jejunojejunostomy between loops to choledochojejunostomy

## CASE REPORTS

## RESECTIONS OF THE BODY OF THE PANCREAS AND SPLEEN

**Case 1**—J L (233821), male, age 32 (Previously reported in detail) The patient had attacks of hyperinsulinism and was explored in another institution in September, 1939, where two tumors in the tail of the pancreas were observed and biopsied, with diagnosis of islet-cell carcinoma. In January, 1940, a large rounded tumor, 15 cm in greatest diameter, was resected together with portions of infiltrated stomach wall and jejunum. There was no evidence of metastasis. He was free from attacks of hyperinsulinism until July, 1942, when these recurred, and in August, 1942, exploratory

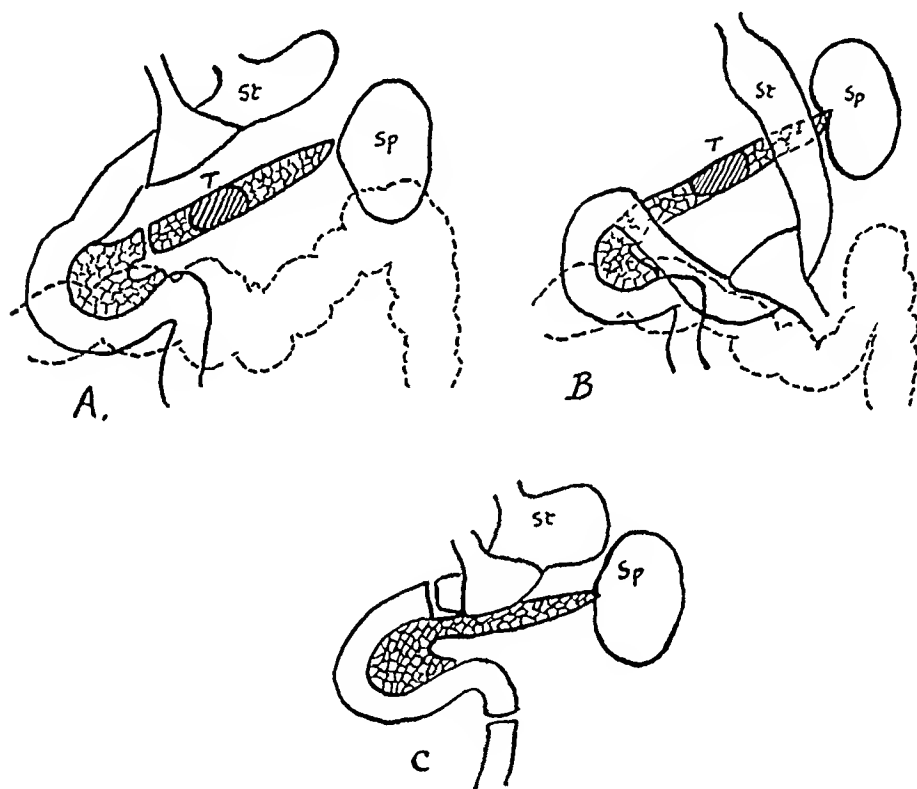


FIG 1—A Schematic representation of excision of body of pancreas and spleen *via* gastroduodenal route. St stomach. Sp spleen. T neoplasm in body of pancreas.  
B Showing access to body of pancreas by downward retraction of redundant stomach.  
C Total pancreatectomy with total duodenectomy and splenectomy. This is followed by gastrojejunostomy and cholechojejunostomy.

celiotomy revealed multiple hepatic metastases—biopsy only was performed. Attacks recurred after a short respite, and from June to December, 1943, alloxan was injected in attempted chemotherapy.<sup>8</sup> The attacks were controlled for periods of three weeks. Finally, at the patient's request another celiotomy was performed to remove the remaining head of the pancreas and what liver metastases could be resected. The portal vein was divided accidentally, necessitating ligation. He died two hours after operation. He survived three years and 11 months after excision of the primary growth.

**Case 2**—P F (162585), female, age 73, was admitted, July 27, 1940, complaining of a mass in the epigastrium and dull intermittent epigastric pain, both noted for two months. She stated that she had had "stomach trouble for 50 years." Examination revealed a firm, rounded mass in the midepigastrium situated over the aorta and transmitting a bruit. Roentgenograms of the stomach were normal. The clinical impression was abdominal tumor of undetermined origin or aortic aneurysm. Celiotomy was per-

formed August 1, 1940 The mass was discovered to be a rounded carcinoma in the body of the pancreas, 4 cm in diameter, near the neck The neck was transected and body of pancreas, with spleen, resected There were a few metastatic nodes in the liver, not exceeding 1 cm in diameter, and several enlarged and firm periaortic lymph nodes Immediate recovery from the operation was satisfactory, but the patient expired suddenly on the third day Necropsy revealed an antemortem thrombus in a branch of the portal vein and several hepatic infarcts There were several old healed myocardial infarcts

Case 3—M K (295967), male, age 66 A physician, in June, 1942, developed constant severe epigastric pain not related to eating or bowel movements Appetite became very poor, and he lost 12 pounds in five months The pain finally developed a high girdle distribution was very severe, especially upon lying down, and became more or less



FIG 2—Case 3 Surgical specimen consisting of entire body of pancreas infiltrated by carcinoma, and spleen

constant. After numerous consultations, he made his own diagnosis of neoplasm of the pancreas Icterus had developed Physical examination was negative except for upper abdominal tenderness Celiotomy was performed November 2, 1942, and revealed a carcinomatous mass in the midportion of the body of the pancreas, with multiple hepatic and peritoneal metastases With the abdomen open it was decided to resect the body and tail of the pancreas in an attempt to alleviate pain The jaundice appeared to be due to intrahepatic obstruction from metastases as the common duct was not enlarged. The surgical specimen is shown in Figure 2 Immediate recovery was satisfactory and there was much less pain during the postoperative period He died five weeks later, cachexia having become very pronounced Necropsy revealed carcinomatosis

Case 4—H D (170446), female, age 55, was admitted September 5, 1943, complaining of generalized fatigue for over a year, periods of nausea and vomiting for one month, and loss of 20 pounds during the past four months, attributed to "dieting" Slight icterus On physical examination, the right lobe of the liver was moderately enlarged but smooth Roentgenologic examination revealed normal stomach, extrinsic pressure narrowing in the upper half of the descending portion of the duodenum and nonvisualization of the gallbladder The clinical impression was carcinoma of the head of the pancreas Celiotomy was performed September 11, 1943 An oval carcinomatous mass, about 4 cm in diameter was found in the proximal portion of the body of the pancreas and extending into the neck It was planned to excise this by pancreatoduodenectomy,

with transection of the pancreas in midportion of the body well beyond the neck. The operation was begun in the usual manner by mobilizing the head of the pancreas and duodenum. When mobilization of the neck was attempted the first portion of portal vein was accidentally opened due to tumor infiltration of an appreciable segment of the wall. Before hemorrhage could be arrested the portal and superior mesenteric veins had been ligated and had retracted some distance from each other. It was felt that the patient would not survive and that termination of the operation as quickly as possible was indicated. Transection of the pancreas through the tumor was carried out to excise

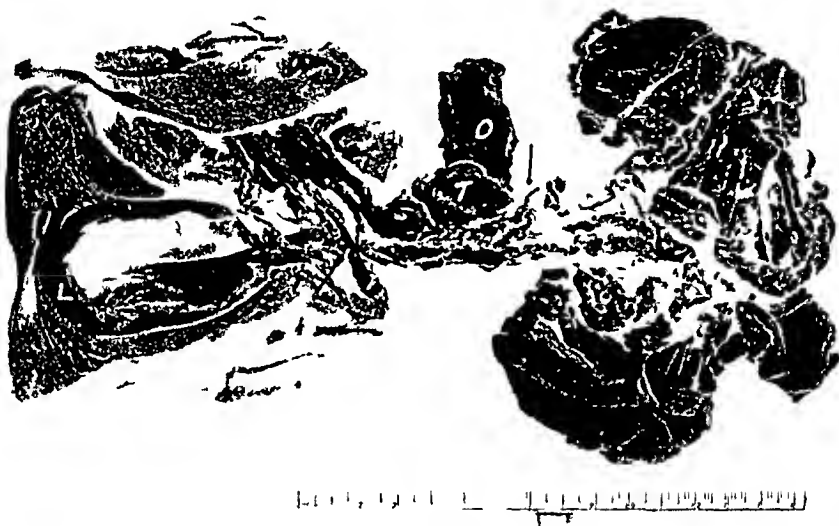


FIG 3—Case 4. Necropsy specimen obtained on tenth postoperative day. L, liver and gallbladder; P, ligated portal vein; O, proximal portion of body of pancreas, with bisected portion of tumor; T, *in situ*; small white arrow to right of pancreas indicates site of ligation of superior mesenteric vein.

the mobilized lower stomach, head of pancreas and duodenum. A gastrojejunostomy was performed and a urethral catheter tied into the transected common duct and brought to the outside through the abdominal wound. The immediate postoperative course was astounding in that recovery was relatively satisfactory. She survived for ten days. Necropsy revealed acute biliary fibrinopurulent peritonitis. She had had a pelvic operation 20 years previously. There were extensive omental adhesions to the lower anterior abdominal wall and in addition to this collateral venous circulation was obvious at the base of the mesentery of the small bowel and in the retroperitoneal spaces. The necropsy specimen showing ligated portal and superior mesenteric veins is demonstrated in Figure 3.

**Case 5**—G. M. (50813), male, age 49, was admitted October 9, 1943, complaining of severe spasms of pain in the back of five months duration, with radiation to each side which was described as affording the sensation of "giant ice tongs" having been applied to his body. There had been loss of 20 pounds weight in four months. Palpation of the abdomen was negative except for moderately enlarged liver. Roentgenologic study of the alimentary tract was negative. The patient had been luetic but had had extensive treatment. The clinical impression was carcinoma of the pancreas. Celiotomy was performed October 11, 1943. A tumor mass, 10 cm. in length and 6 cm. in width, was situated along the superior border of the pancreas and apparently arising from this organ. No metastases were apparent. Resection of the body of the pancreas and spleen together with adherent left adrenal gland was carried out (Fig. 4). There was diffuse but not marked cirrhosis of the liver and this organ was biopsied. Immediate convalescence was satisfactory. Pain was completely relieved. He was discharged on the 20th day. At home,

## CARCINOMA OF PANCREAS

he did not continue to improve, icterus developed and became progressively worse. Weakness became more pronounced and there was loss of appetite. He succumbed November 18, 1943, five and one-half weeks after operation. Necropsy revealed large intrahepatic metastases not appreciable on the surface, situated just within the porta hepatis and occluding the right and left hepatic ducts.

**Case 6**—C P (325186), female, age 55, was admitted, January 12, 1944, complaining of "gas pains" in the left upper quadrant and pain in the region of the umbilicus, with radiation through the body to the back, two months duration. She stated she had had "stomach trouble all of her life." There was loss of 20 pounds weight in the past



FIG 4—Case 5 Surgical specimen consisting of entire body of pancreas with large carcinoma (T) arising from upper border, and spleen

month. Physical examination revealed marked tenderness in the upper abdomen and a firm tender nodule within the umbilicus, suspected of being a metastasis. Cholecystograms revealed nonvisualization of the gallbladder. The clinical impression was possibly carcinoma of the gallbladder. Celiotomy was performed on January 15. The lower portion of the stomach was studded with metastatic nodules as was the falciform ligament and deeper aspect of the umbilicus. In the wall of the lesser curvature of the stomach there was an oval, firm area assumed to be malignant neoplasm. In the distal portion of the body of the pancreas there was an oval, firm mass, 4 cm in greatest diameter, obviously carcinoma. The liver and peritoneal surfaces were free from metastases. The gallbladder wall was slightly thickened and it contained numerous small stones. A subtotal gastrectomy was performed leaving about one-sixth of the stomach. The spleen was then mobilized and used as a handle to elevate the body of the pancreas. The latter was transected about 3 cm distal to the neck, with resection of tumor-bearing portion of pancreas and the spleen. The stump of pancreas was closed with interrupted interlocking silk mattress sutures. A Polya gastrojejunostomy was performed. The falciform ligament and umbilicus with surrounding tissue were excised (Fig 5). The gallbladder filled with small stones was not removed. Convalescence was rather stormy due primarily to failure of function of the gastro-enterostomy. The patient however was sustained by glucose, casein digest, and gelatin intravenously, and eventually improved. She was dis-



charged on the 44th day after operation, able to partake of general diet, free from pain, and in fair general condition. Three months after operation her condition remains relatively satisfactory. There is no abdominal pain, she is able to eat a varied diet and is ambulatory.

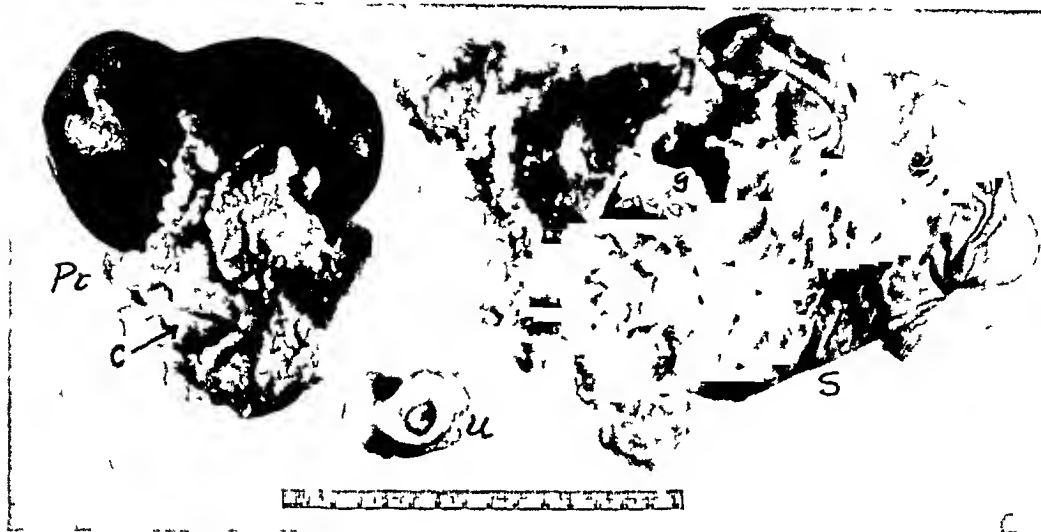


Fig 5—Case 6. Surgical specimen consisting of Pt distal portion of body of pancreas with carcinoma (C) and spleen. S, lower 5/6 of stomach resected because of serosal metastases from pancreatic neoplasm. G, large metastasis which at operation was thought to be primary carcinoma in stomach. U, umbilicus and falciform ligament containing metastases.

#### TOTAL PANCREATECTOMY

**Case 7**—H H (302199), male, age 67, was admitted, February 24, 1943, complaining of loss of 40 pounds weight, diarrhea, continuous upper abdominal pain of five months duration, icterus for two months, with severe pruritis, and pain in the chest, cough, edema of ankles, and hoarseness of two weeks duration. Physical examination revealed dullness and absent breath sounds in the left thorax, the abdomen was negative except for a moderately enlarged and smooth liver and questionable fluid wave. Icteric index 115. Roentgenograms of the chest showed massive left hydrothorax. The stomach and colon were normal. Left thoracentesis was performed (625 cc of bloody fluid), on February 22. Celiotomy was performed February 26, 1943. The entire pancreas was found extensively indurated by carcinoma, there were several hepatic metastases. Total pancreatectomy, total duodenectomy and splenectomy with gastrojejunostomy and cholechojejunostomy were performed. Immediate recovery was satisfactory but the patient succumbed on the third day. Necropsy revealed massive bilateral pulmonary consolidation as the immediate cause of death.

**Case 8**—N R (309791), male, age 29, was admitted, May 20, 1943, because of 40 pounds weight loss in four months, upper abdominal pain, more or less constant, and increasing in severity, three months, increasing icterus and pruritus, two months. Physical examination was essentially negative except for upper abdominal tenderness, moderate enlargement of the liver and severe icterus (icteric index 159). Celiotomy was performed May 27, 1943. The pancreas was diffusely involved by carcinoma, there were no hepatic metastases. Total pancreatectomy, with total duodenectomy and splenectomy, gastrojejunostomy and cholechojejunostomy were performed. Immediate recovery was satisfactory, but after the second day the course was rather stormy. Less insulin than anticipated was required. The details of the postoperative course from this standpoint will be reported elsewhere (Goldner and Clark). He succumbed on the ninth

CARCINOMA OF PANCREAS

day Necropsy revealed metastases to mediastinal lymph nodes, suprarenals, both kidneys, a small perforation of the common duct from which there was a sinus to the abdominal wound; bilateral partial atelectasis, in short, the patient died of exhaustion

A summary of the results in the above series of patients is given in Table I

TABLE I  
RESECTIONS OF THE BODY OF THE PANCREAS AND SPLEEN

Case No	Pathologic Condition	Course
Case 1	Islet-cell carcinoma invading entire body	Lived 3 years, 11 months Died after 3rd celiotomy as a result of portal vein ligation
Case 2	Carcinoma proximal portion of body Few hepatic metastases	Died 3rd day (portal thrombosis?)
Case 3	Carcinoma invading entire body Multiple hepatic metastases	Lived 5 weeks Died of carcinomatosis
Case 4	Carcinoma of proximal portion of body and neck	Lived 9 days Died of bile peritonitis Portal vein ligated
Case 5	Carcinoma arising in upper border of body	Lived 5 1/2 weeks Died of "exhaustion Necropsy revealed single large intrahepatic metastasis
Case 6	Carcinoma of tail of pancreas with metastasis to stomach and retroperitoneal lymph nodes	Living 3 months after resection of body of pancreas and radical gastrectomy Evidence of recurrence
TOTAL PANCREATECTOMY AND DUODENECTOMY WITH SPLENECTOMY		
Case 7	Entire pancreas replaced by carcinoma Metastases in liver	Died 3rd day Massive bilateral lobar pneumonia
Case 8	Entire pancreas replaced by carcinoma Metastases in liver	Died 9th day of "exhaustion "
Immediate operative mortality, 50% (4 cases)		
Survivals 4 cases, 5 weeks 5 1/2 weeks 3 years 11 months one living 3 months in fair condition respectively		

SECONDARY INVOLVEMENT OF BODY OF PANCREAS

Neoplasms arising in viscera adjacent to the body of the pancreas may involve the latter by direct extension This does not constitute a contraindication for excision of these growths since resection of the body and tail of the pancreas *en masse* with them is quite feasible The author has performed total gastrectomy, with splenectomy, transverse colectomy, and resection of the body and tail of the pancreas for carcinoma primary in the stomach The patient survived six months, with a period of symptomatic improvement In another patient a large adrenal (left) carcinoma, 20 cm in diameter, infiltrating the under surface of the left diaphragm, the muscles of the left posterior abdominal cavity, the hilum of the spleen, about the upper pole of the left kidney, and the posterior surface of the body and tail of the pancreas, was resected *en masse*, with its extensions, including the under surface of diaphragm, body and tail of pancreas, *etc* The patient is living and well, without evidence of recurrences two years later He is at work full time as a draughtsman A third patient with a very large carcinoma of the splenic flexure infiltrating the stomach, hilum of the spleen, and body of the pancreas was recently subjected to successful resection of the lower three-fourths of the stomach, together with body of the pancreas, spleen, most of transverse colon, and upper two-thirds of descending colon Other cases of excision of portions of the body of pancreas with neoplasms arising in adjacent organs have been reported elsewhere<sup>9</sup> The success of massive resections as described above is dependent, to a large extent, upon the liberal use of blood transfusions Transfusions are begun at the out-

set of the operation and continued as needed to maintain a systolic pressure of 100 Mm of mercury. Quantities of 2000 to 3000 cc are sometimes necessary and must be employed without hesitation. Plasma transfusions alone do not suffice.



FIG 6—Case 8. Surgical specimen consisting of entire pancreas infiltrated by carcinoma, spleen, lower stomach and entire duodenum. Arrow indicates duodeno-jejunal junction.

**DISCUSSION**—In six of the eight patients subjected to partial or total pancreatectomy, metastases were apparent at the time of operation. What, then, was the justification for the operation? With the abdomen open it was felt that the primary growth should be resected as a means of palliation since in all of these patients (except Case 1) constant severe pain was an outstanding complaint. The pain of cancer of the body of the pancreas is characteristically severe, non-colicky, and more or less constant, and its amelioration would constitute a degree of palliation. Appreciable amelioration of pain was actually accomplished in Cases 3, 5 and 6. However, the question remains, principally of academic interest, whether such relief was afforded by the removal of the cancerous pancreas, or by the extensive division of sympathetic nerves which such operations entail.

The results obtained in the above series of patients are far from encouraging. The great difficulty in this field lies in the fact that patients are not subjected to celiotomy early enough in the course of the disease to permit of complete excision by radical resections. Cancer of the body of the pancreas is, indeed, a silent lesion in its earlier development (except when it may arise in the neck and proximal portion of the body and produce icterus, as in Case 4). It is removed from the alimentary and biliary tracts and, therefore, does not produce obstructive symptoms early. With exception of Case 1 (insulin-pro-

ducing islet-cell carcinoma) the above patients' serious complaints were of two, five, four, five, two, five, and four months duration, respectively, an average of three and eight-tenths months. Early in these periods it would appear to have been hardly justifiable from the histories as given, to make the diagnosis of carcinoma of the body of the pancreas and advise operation. There is no purpose to be served by repeating here the classical signs and symptoms of carcinoma of the body of the pancreas, since these are well known and when present the patients usually are in an advanced stage of the disease. As mentioned in a previous communication, there is perhaps some parallelism between the present situation surrounding the surgery of cancer of the pancreas and the situation of gastrectomy for carcinoma of the stomach during the quarter century following Billroth's first successful pylorotomy. Relatively few patients were subjected to partial gastrectomy during this period and the large majority of the patients who underwent exploratory celiotomy for gastric cancer were considered inoperable. Indeed, the future of gastrectomy for cancer was not considered very bright by some authorities of that period. It is hoped that, with the feasibility of radical pancreatectomy now well established, persistent efforts will result in a more hopeful future for this particular branch of surgery than would appear to be justifiable on the basis of experiences up to the present time.

#### SUMMARY

Cancer of the body of the pancreas is manifested clinically late in the course of the disease. While radical resection of such neoplasms is feasible, few patients are subjected to operation early in the evolution of these growths.

Six instances of resection of the body of the pancreas with splenectomy and two instances of total pancreatectomy, with total duodenectomy and splenectomy, are recorded. The immediate operative mortality was 50 per cent (four cases, including the two total pancreatectomies). One patient with islet-cell carcinoma invading the entire body and later manifesting hepatic metastases lived three years and 11 months. Of the remaining three, two survived five weeks and five and one-half weeks, respectively, had metastases at the time of operation, but experienced appreciable amelioration of severe abdominal pain. The third is living, comfortable, and in fair general condition three months following resection of the body for carcinoma and subtotal gastrectomy for metastases to the stomach. Metastases to the falciform ligament and umbilicus were also resected.

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DISCUSSION—DR ROY D McCLURE, Detroit, Mich I wish to report a successful case of total pancreatectomy for primary carcinoma of the pancreas, showing the feasibility of Doctor Brunschwig's experience

A 46-year-old male was admitted to the Henry Ford Hospital, January 2, 1944, for treatment of painless obstructive jaundice A diagnosis of probable carcinoma of the pancreas was made on the basis of the history of gradually deepening jaundice, plus the presence of a palpable mass in the midepigastrium in the region of the pancreas

Celiotomy by my associate, Dr Lawrence Fallis, was performed, January 14, 1944, under nupercaine anesthesia A transverse incision was made in the transpyloric plane Exploration revealed a distended gallbladder, a dilated common duct, and an enlarged pancreas which was indurated throughout

A one-stage, complete pancreatectomy, duodenoctomy and splenectomy was performed Section showed carcinoma of the pancreas Restoration of the continuity of the intestinal tract was by terminolateral gastrojejunostomy, with implantation of the common duct into the jejunum proximal to the anastomosis

The patient left the hospital on the 23rd day after operation, following an uneventful postoperative course He returned to part-time work two months later His insulin requirements have been 26 units of protamine insulin daily, supplemented about twice weekly by 8 units of regular insulin

This patient was shown in our clinic one week ago today His jaundice has entirely disappeared His strength is improving, and he has the appearance and mental attitude of a healthy normal man Doctor Fallis is continuing his studies of this case Not so many years ago we thought the pancreas an essential organ

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## THE REPAIR OF SURFACE DEFECTS OF THE FOOT\*

LT COL JAMES BARRETT BROWN, M C , A U S

AND

CAPT BRADFORD CANNON, M C , A U S

THE SKIN AND SUBCUTANEOUS TISSUES of the sole of the foot (and of the palm of the hand) constitute a specialized organ, similar structure does not occur elsewhere in the body, and it is a congenital structure—not a developmental one. Covering, transplanted in the sole from other areas of the body, does not metaplaste to become a normal sole—simply walking on the new tissue will not cause it to change into a normal sole. The opposite may be true, and there may be difficulty in maintaining a satisfactory condition of tissues transplanted to the sole. Keratosis, warts and cracks, may require frequent attention, and chronic ulcers may occur. It might be said that only substitutions can be made for losses of the sole.

By recognition of the importance of the intact sole of the foot, so that interruptions of its surface are kept to an absolute minimum in surgical procedures, and so that adequate repairs are designed and carried out when necessary, much morbidity can be avoided. The importance of a normal sole of the foot is often overlooked just as the skin covering of the body is not thought of much, until it is diseased or has been lost. In the foot the comparison might be the difference one experiences in not having and in having a tack in a shoe. Just as soon as the intact sole is opened, trouble and disability begin, and they continue until there is complete permanent healing.

The covering is also specialized around the heel and heel cord—over the dorsum it is not so much so, but the important subcutaneous tissue over the malleoli and the dorsum must have intact surface covering, to perform its function of resistance to trauma.

*The sensory nerve supply* on the foot is of great importance too. When there are anesthetic areas, and especially if they are in scarred or repaired areas, there is constant danger of trauma and chronic ulceration. In dealing with large number of patients it seems apparent that intact sensation in the foot is close, in relative importance, to that of the cornea and the hand. Sensation will return, if the nerves are present in the area—even to free grafts.

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\* Presented by title before the American Surgical Association, May 3-4, 1944, Chicago, Ill.

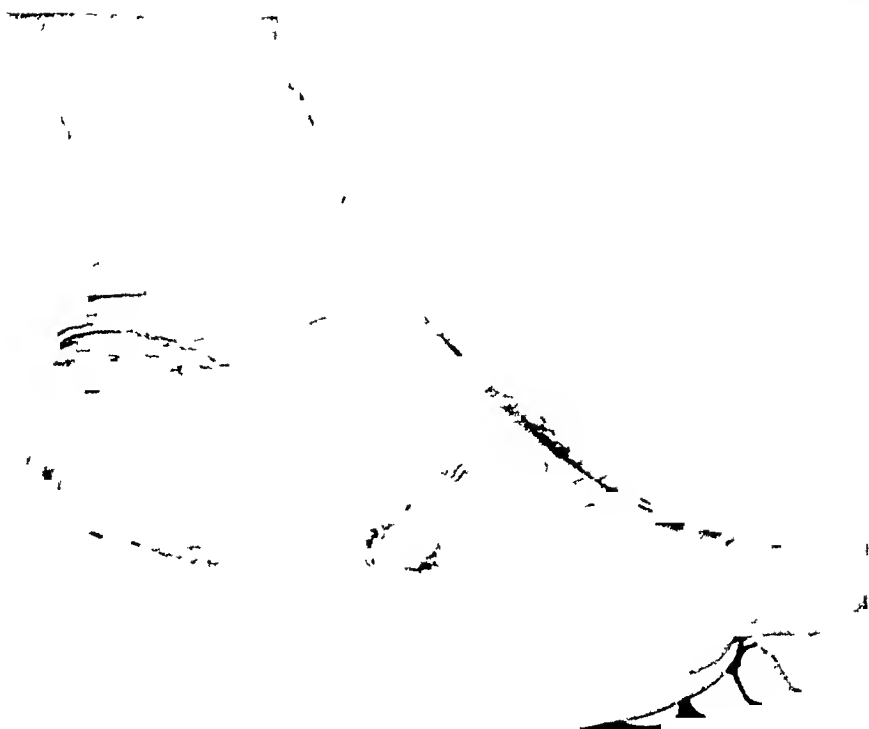


FIG 1—Small insignificant looking graft put on after resection of painful scar. Soldier had been returned to Z. I., and was ready to give up because of discomfort. Following relief of pain and healing with the thick split graft he requested return to duty. One operation.



FIG 2—Traumatic loss of forefoot with skin loss over rest of foot. Patient came in for amputation. Completely covered in one operation with thick split skin grafts. Persistence of function after six years: patient pursues all normal activities, but has some annoying keratosis and requires care and protection.  
From "Skin Grafting of Burns," Brown & McDouell, J. B. Lippincott, 1944

and flaps, but if the nerve does not get into the area, permanent anesthesia will result. The regeneration of sensation is often such a slow process that it is impossible to keep the patient in bed the whole time—but the first display of carelessness with an anesthetic foot will result in ulceration and trouble.

Even small lesions on the foot may produce complete and prolonged disability, as any one can attest who has had a painful wart. And these small lesions in military services are capable of much waste of man power. It is recognized, that a small lesion on the foot, that would go unnoticed in civilian life, may cause complete loss of service in a soldier, because one of the most important functions is that the soldier be able to walk. Small lesions have been observed to have kept soldiers off duty over a year, and one, with ulcers over the shins, was off duty through a nine-year period.

These small lesions may be undramatic, and seem little, in the over-all picture of war wounds. Their repair may seem insignificant, but may be most difficult to accomplish, and finally may mean a very great deal to the patient (Figs 1, 5 and 6).

The commonest causes of trouble are shell fragment and gunshot wounds, burns, traffic accidents, warts, decubitis, radiation, and cold injuries.

*Preoperative care* is necessary for any type of operation, and includes rest, baths, soap and water, sulfonamides or penicillin, fine-mesh gauze next to open wounds, cotton mechanics waste, or latex-foam pressure dressings, and elastic bandaging of the foot and leg. Bacterial studies are made on chronic ulcers and every effort is made to get them as clean as possible. No repair or operations need be contemplated until all sloughs, dead tendons, fascia and bone are out of the wound, and there is a good tendency to healing and the development of a minute blood supply that will support the transplanted tissue. Physical therapy procedures are used in practically all patients. Inflammation and edema of the foot or leg are contraindications and the same criteria are necessary for flaps and grafts. Flaps do *not* need less careful preparation—in fact, they require the closest attention to detail because loss of one is more serious than loss of a free graft. Patients have been seen with lost flaps and with the donor site of the flap worse than the original lesion.

*Resection of Scars*—Scars of widespread lesions of gunshot wounds may be exceedingly dense and deep, and leave small chance of arriving at a normal minute blood supply. This is still more true of radiation lesions, so that apparently radical procedures have to be carried out to give any chance of survival of the transplanted tissue.

Several different methods of repair of these lesions are available and are fitted to individual patients.

Burns and superficial losses are often amendable to free grafts here—as in other areas of the body (Fig 4), but gunshot and shell fragment wounds, and other deeply scarring injuries, often require some type of flap repair.

*Grafts versus Flaps*—Flaps are not apt to do well where grafts will not, at least, take and survive. Flaps must attach throughout the whole extent of the wound, and although much of their blood supply may come from edges,



there must be firm healing throughout the full base of the lesion, or the flap will be detached, and troublesome sinus formation will persist and make the repair practically useless. A distant flap does not bring in any additional blood supply, but just helps the local, minute supply secondarily, after the

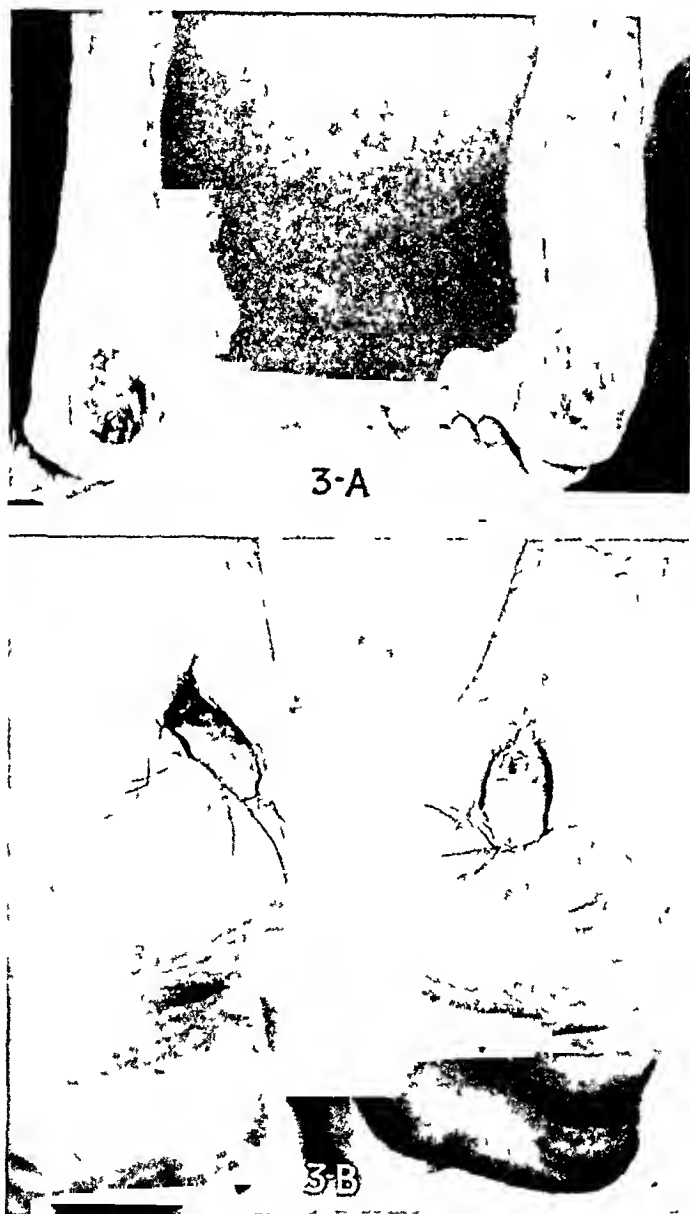


FIG 3—Decubitus of both heels (also sacrum and elbow in same patient). Healed by "dressing" areas in thick split grafts. One operation.

scar has been excised for the reception of the flap. Local flaps, on the other hand, do bring in their own blood supply and can be relied upon actually to improve the local circulation. The necessary caution about the use of local flaps is that they may deprive another area of needed covering, and they may cause loss of important local sensory nerves (Figs 7, 8, 9 and 10).

*Bearing points* and "silent" areas are of extreme importance, and local

flaps should not be designed that uncover important weight bearing points or the heel cord, or malleoli, so that these areas, in turn, have to be covered with inadequate skin grafts. When more or less "silent" areas can be utilized for local flaps they find their best application, but it is important to remember that when a flap is used that its bed nearly always has to be repaired (Figs 5, 6 and 7)

*Methods*—(1) Excision of scars or lesions and resuture can be undertaken only occasionally, because there is little or no extra tissue in the foot. Care must be taken in deciding on this procedure—especially over the heel

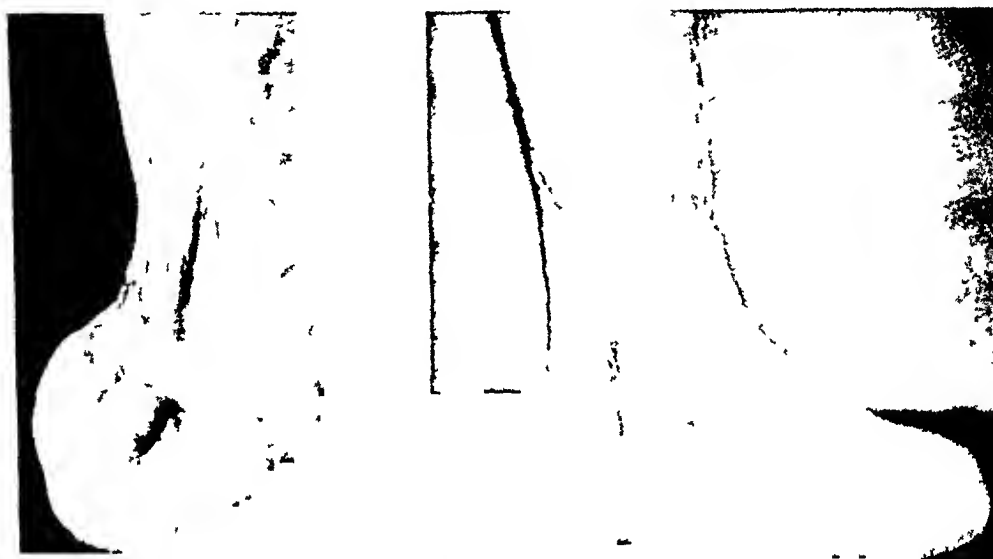


FIG 4—Painful deformity from old burn, complete restoration of function from one thick split graft operation, persisting after nine years  
From "Skin Grafting of Burns," Brown & McDowell, J B Lippincott, 1944

cord and on the sole. This procedure can be employed when there has been a partial amputation and what amount to adequate flaps have been preserved. But as a general rule the sole of the foot is not subject to excision and closure and primary healing. Neither will it give satisfactory healing if large areas are lost and closure by granulation and scar epithelium is allowed to occur. Large losses nearly always need some type of replacement even if the replacement is a rather poor substitute.

(2) Free skin grafts are used if a satisfactory thickness of subcutaneous tissue remains to give support and blood supply. Grafts, of course, will not grow on bare cortical bone, or bare tendon or fascia. When free grafts are used, good thick split-grafts usually suffice and they preferably should be taken from hairless areas. One important use of grafts is to get wounds healed quickly even if it is recognized that the graft will not be a final restoration. This has been designated "dressing" wounds in thick split-grafts. Open wounds on the sole of the foot are subject to recurrent, and severe and disabling infections. If these lesions can be carried along, at least, in a healed condition, there is improvement in the minute circulation, and there also is given information as to whether a flap will grow in the area. It can be repeated, that flaps are not apt to do well where free grafts can not grow (Figs 1-10)

(3) *Direct local flaps* either shifted laterally, or rotated, with immediate graft of the donor site, may give excellent repairs of small lesions, if one can meet the elements of caution in the procedure. These elements are not interrupting important sensation, and, of course, being sure of the adequacy of the local blood supply for healing, and of the blood supply of the flap itself. It is extremely important not to cut the pedicle of the flap for smoothness sake, but the opposite should be done, *i e*, leave the pedicle prominent and clear out of position if necessary, and do a secondary smoothing out later (Figs 5 and 6).

(4) *Delayed local flaps*, shifted laterally or rotated. This is the safest form of flap to use locally and should be raised in at least two stages, making the lateral cuts, undermining and carefully closing the flap first, and, at a separate stage, cutting across the distal end of the flap and closing it. These flaps should not be used until there is complete healing, no inflammation and no swelling. The lesion itself is not excised until the flap is ready for use, and for this reason, the primary design of the flap is made large enough for the largest possible opening of the defect (Fig 7).

*Cross Leg Flaps in General*—In all cross leg flaps sensory nerves and pressure points have to be avoided, and, in general, the lower leg is not very satisfactory because of lack of tissue in "silent" areas, and because the resultant defect of a flap from the lower leg may be difficult to repair satisfactorily. The circulation of the lower leg has vagaries that need to be carefully considered. An unhealed donor site of a cross leg flap may give as much trouble as the original lesion.

When a flap is used, the essential reason is to get extra thickness in the subcutaneous tissue, but it should be noted whether or not a lower leg *has* the desired type of tissue available.

If a patient has a badly crippled foot or leg and the repair is going to be only a partial restoration, then there should be added caution and consideration before cutting into the one remaining good leg, which is going to have to do most of the work anyway.

Cross sole of foot flaps are not advocated because of being difficult to carry out, of limited usefulness, and because of the possible partial crippling of the donor foot.

Grafting the donor site of a flap can be done when it is put up if desired and this gives a cleaner wound to take care of. There will usually be some further grafting to do when the flap is detached, however, and the total repair of the donor site is sometimes left until the flap has been severed. It is usually necessary to perform a careful excision of granulation and scar from the donor site and cover the defect with a thick split-graft, especially if the lower leg has been used.

*Fixation* of cross leg flaps can nearly always be accomplished with adhesive and padding and pillows, and with foam-latex or neoprene (synthetic rubber) over pressure points. Plaster encasements or supports are necessary at times, and may be prefabricated and then joined with more plaster at

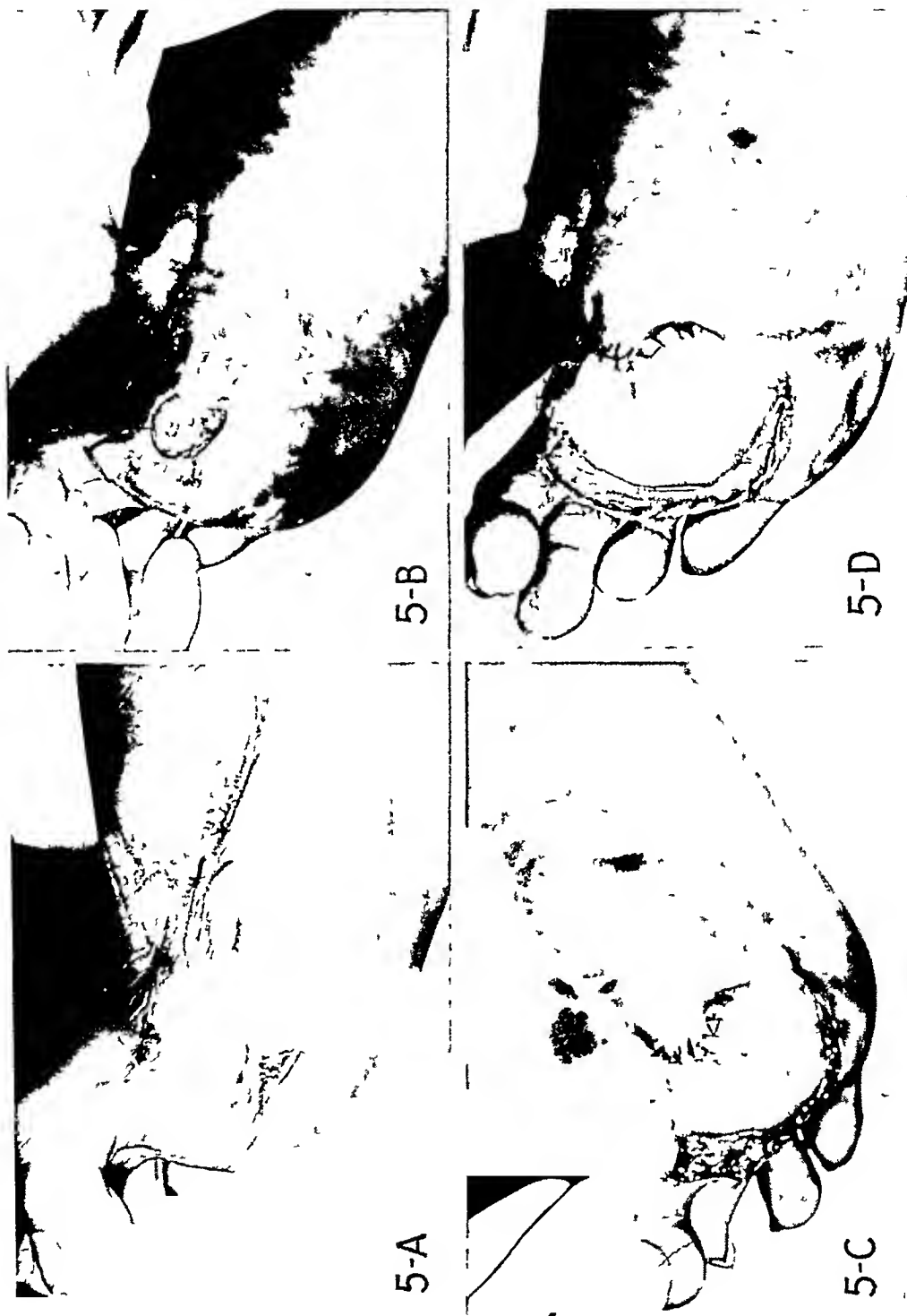


FIG 5—Gunshot injury with painful hard scar preventing use of remaining bearing surface over second metacarpal. Repaired with immediate, direct, local, rotated flap from behind toes and closure of defect in "silent" areas with thick split graft. One operation

operation Adjustment of position within plaster is more difficult than with adhesive

Detaching flaps can usually be undertaken in 16-20 days If the flap is a large one, partially detaching it in two or three stages can be done with more safety If much of a flap has to be used to complete a defect, such as going

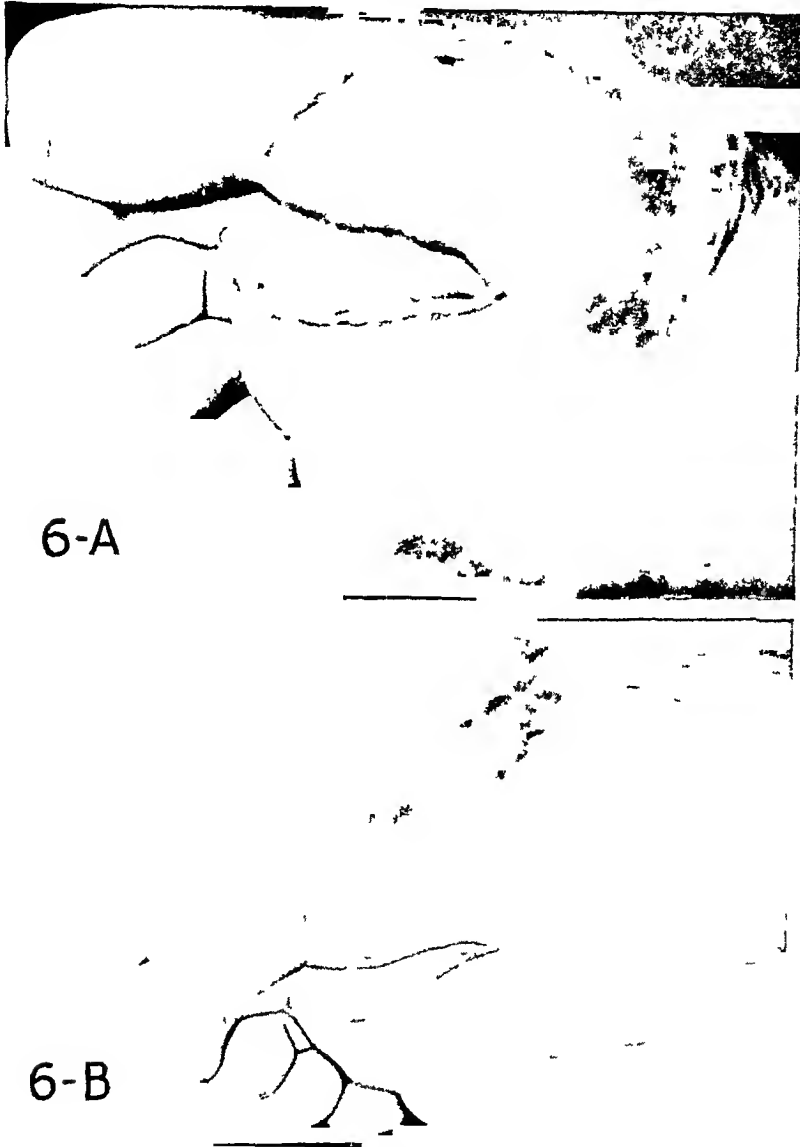


FIG 6—Result of utilizing relatively silent area to repair weight bearing area The shell fragment wound over the bill has been excised, a direct flap from the center has been rotated into position, and the flap donor site healed with a thick split graft One operation

clear around both sides of a heel, it is sometimes advisable to undertake a secondary delay procedure on this part of the flap while the first part is still attached

(5) *Direct cross leg flaps* from the opposite thigh or calf can be used for many defects, large or small, if a suitable position can be decided on, and the patient is capable of accepting the distorted life for the necessary 16-24



FIG. 7.—Defect plus scar about malleolus that would probably not carry either a free graft or a distant flap. Local debrided, rotated flap used to carry its own blood supply. Donor site carefully covered with thick split graft. Whole area, firmly healed, and with adequate care will give satisfactory function. First operation. Flap raised and undermined. Second operation. Flap cut across distal end. Third operation. Flap shifted after excision of scar, and donor site grafted.

days The direct flap can not be used, if the base can not be swung out wide enough to insure blood supply or if the lesion can not be gotten close enough to the donor area so that a relatively short pedicle can be used (Figs 9-10)

(6) *Delayed cross leg flaps*, either flat or tubed, are the safest kind to use

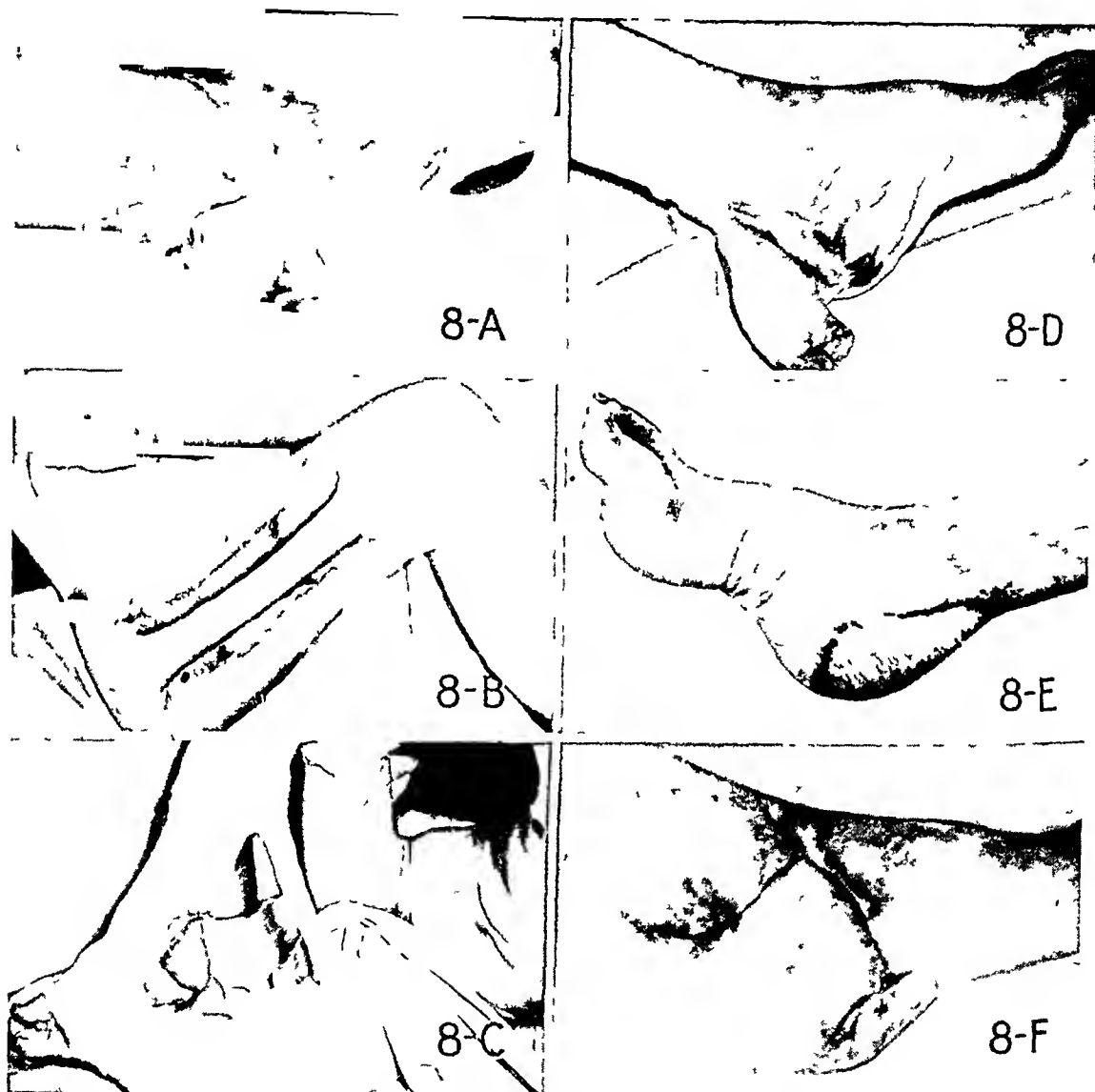


FIG 8—A Deep, solid scar around heel, chronic ulcer healed after being "dressed" with a thick split graft, as best preparation for the wound and area to receive flap

B Tubed flap, repaired in single stage, and defect grafted rather than trying to pull it together, or leaving it open

C Fixation of cross leg position

D Flap off

E and F Completed flap, with wide restoration of region

(As in all plastic procedures when shifting tissue, the division of the work into stages is the surest way) It can be noted that cutting clear around three sides of a flap, undermining it, and then resuturing it in its bed is *not* delaying it as far as its blood supply is concerned It should be outlined along

two sides, undermined and closed and at a later date, 10–20 days, have the distal end cut and resutured and then not used until there is complete healing and normal softness of the tissues (Fig 8)

(7) *Same leg delayed flaps* can be used occasionally, usually tubed rather than flat ones, but this entails complete change of direction to get to the foot, and little is gained except avoiding the cross leg position, and the possible crippling of the opposite leg. It is an important consideration when the opposite leg is missing.

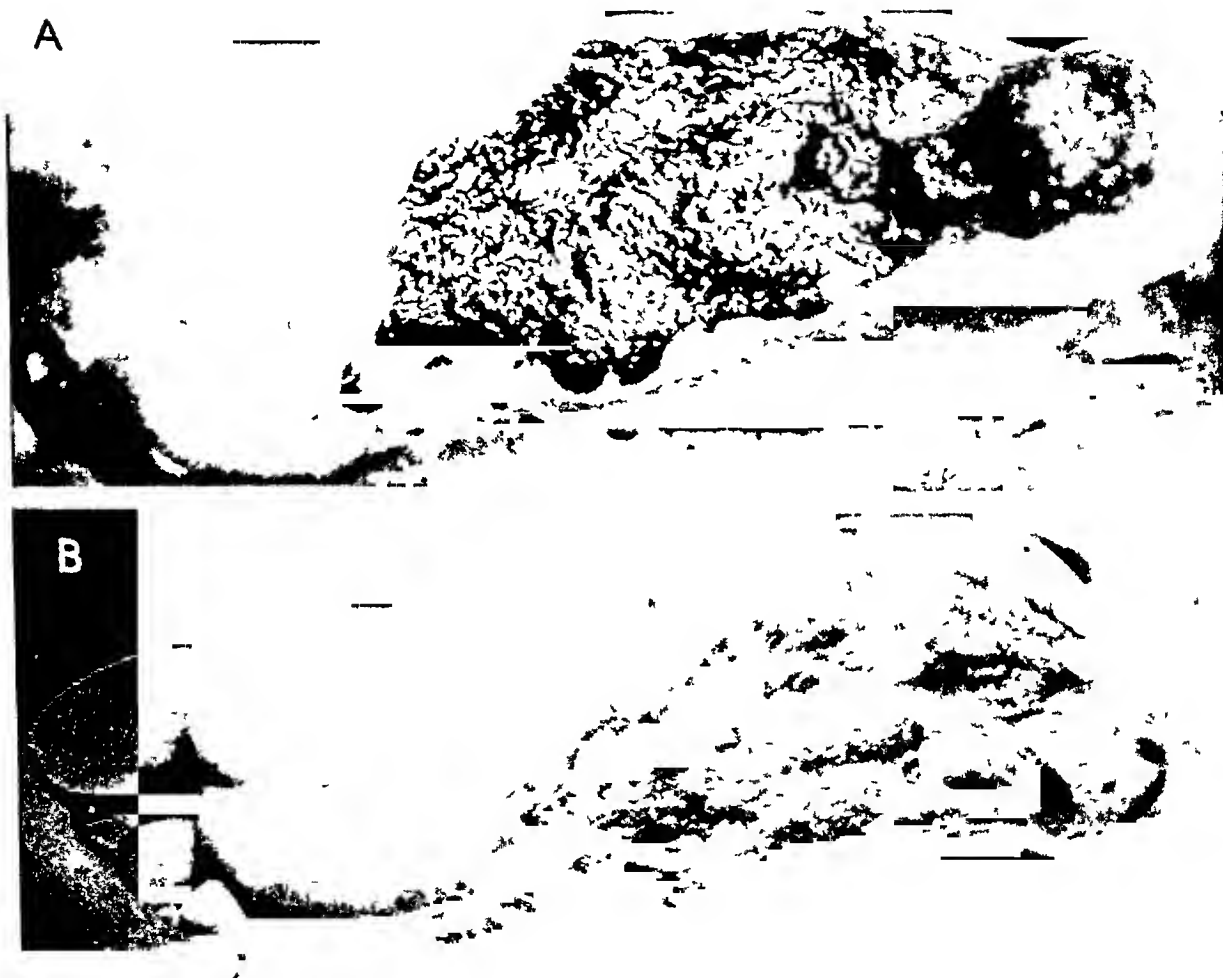


FIG 9—A Extensive loss of sole of foot.  
B Split graft applied as “dressing” to supply quick healing, but obviously insufficient pad for patient to walk on.

(8) Distant “turn-over,” “jump,” or “caterpillar” flaps from the abdomen or flank are of rare necessity, require a long time in completion, and usually waste a large amount of flap. They are occasionally useful if the other leg is missing.

(9) Distant wrist-borne flaps are utilized by some surgeons, picking up an abdominal or flank flap on the wrist and carrying it to the foot. This is of limited usefulness but may give an excellent repair if enough time can be spared, because there is a wide range of selectiveness of tissue in this method.

Tubed flaps need one special mention of application, *viz*, a large, long





FIG 10—A Direct cross leg flap applied later, when patient in Figure 9 had fully recovered from accident  
 B Good functioning sole, which allows patient to get around normally, but which requires care  
 Able to play baseball  
 C Grafted donor site on thigh. First grafted when flap was put on foot—remainder grafted when foot was taken off. Graft taken off sole of foot was used on this area, that had originally come from the opposite thigh

From 'Skin Grafting of Burns', Brown & McCordell, J B Lippincott 1941

tube often had best be attached in a normal site close to the defect. Then when detached from the donor site, put in a second normal site close to the other end of the defect so that a sort of a suitcase handle of good tissue is lying close to the defect—getting its blood supply from two good sources. Then when the flap is established locally it can be opened and completely applied to the defect after the scar has been widely excised. It still gets its blood supply on both ends and these can be smoothed out when it is firmly established in its new bed. This is a rather long way around but is highly preferable to putting a tubed flap directly into a freshly dissected scar bed and then finding it unable to maintain a sufficient blood supply for the flap.

A tube flap may be more easily applied than a direct or delayed flap flap, because the pedicle can be swung around into different positions more easily than a flat pedicle, and this is especially true if complete healing has occurred under the tubed flap and at its ends. So that if a difficult position is going to be necessary in attaching the flap, that will be made easier if the flap is tubed rather than flat, then this method can be followed.

*Pressure dressings* postoperatively are important for grafts and flaps. Flaps are protected with firm adhesive (or plaster) fixation to prevent troubles with the pedicle, and then a cotton mechanics waste pressure dressing is put over the flap to provide firm pressure on the bed of the defect and to prevent stagnation of venous blood in the flap. This dressing is arranged so that it easily can be opened and the flap inspected as necessary, which should be an hour or so after operation and later in the day. Adjustments of the pedicle may be made, as desirable, by this attention.

*Postoperative care* of tissue transplanted to the foot—whether free graft or flap is very important. One of the worst difficulties is keeping the patient off of the new repair long enough. Theoretically, they should not be on the feet until there is complete healing and complete return of sensation. Constant effort should be made by the patient to prevent trauma—or rubbing of a shoe or brace, and to avoid extremes of temperature. Padded or cut-out shoes are needed frequently, plus the use of crutches or cane if the repair is in a weight-bearing area, or where a shoe may rub.

A soldier simply can not go back on full duty soon after a large foot repair, and to do so usually means further morbidity after the first hike.

Along with postoperative care should go a knowledge of the faults of flaps and grafts so that they can be guarded against. The foremost is the failure to metaplaste into normal foot tissue, and the necessity of continual protection in the form of cleanliness, frequent careful observation for blisters and infections, and the use of foam-latex or neoprene pads in the shoes. Grafts may develop sebaceous collections that should be emptied before they enlarge and become infected. Little bridges of skin may also occur and these should be carefully cut away to prevent infection about them and ulceration. Dried sebum and crust formation also may lead to ulceration and the frequent use of massage and cold cream or lanolin will help keep the areas soft. Where the thin soft repair joins the hard keratotic normal sole, there may be exces-

sive keratosis and even annoying wart formation of the repair. Prevention is much better than cure, by careful cleansing, attention and the nursing that has been mentioned above.

These faults of grafts and distant flaps have led some surgeons to the opinion that only sole tissue should be used on the sole—even if a cross sole flap has to be used, but the difficulty is not as great as this concept. Certainly, in a large series of repairs there would be much more total debility from cross sole flaps than from more distant ones, although it is recognized that the cross sole type may be indicated in occasional instances.

Results of repairs of the foot vary from poor to practically normal lives being led by the patient. Dramatic relief from painful lesions may be had by simple direct flaps or even grafts. Prolonged debilitation, upward to nine years, has been relieved by single procedures, and the essential steps are to get the lesion removed, the defect repaired and healed, and then have the patient cooperate in every way to protect the repair from trauma. The foot and its sole is an area of the body to recognize as one of design and benevolence, that can only be substituted for, once it is lost. Most soldiers with moderate surface defects of the foot can be returned to limited duty.

# REFRIGERATED SKIN GRAFTS<sup>1</sup>

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WHILE BARONIO,<sup>1</sup> in 1804, in his classic experiments, successfully removed full-thickness skin grafts from sheep and allowed varying periods of time up to one hour to elapse before replacement, this knowledge was not utilized clinically until after 1872, when Reverdin,<sup>2</sup> Ollier,<sup>3</sup> Thiersch,<sup>4</sup> and Wolfe<sup>5</sup> reported clinical success with the free skin grafts bearing their names

Girdner,<sup>6</sup> in 1881, claimed to have been the first to transplant skin from a cadaver as a homograft, although without success The following year Brewer<sup>7</sup> reported success with grafts taken from cadavers and amputated limbs up to 36 hours after removal Other investigators have also used skin from these sources

Wentscher,<sup>8</sup> in 1903, was the first to refrigerate free skin as autografts—one for seven days and three for 14 days, all but one of the last were successful Carrel,<sup>9, 10</sup> after experimenting with various media for preserving refrigerated skin grafts, concluded that vaseline was the most satisfactory In 1911, he suggested to surgeons that refrigerated skin might well be used clinically to advantage In 1930, Kubányi<sup>11</sup> in his experiments found that autografts preserved in the individual's serum, if applied after 12 days from date of removal, could live at least eight days after transplantation

Most of the reports to be found in the literature on the use of refrigerated skin grafts are experimental A large proportion of the clinical observations reported deals with the use of homogenous skin grafts from cadavers or from amputated limbs which grafts *cannot be expected to survive permanently*, only a few autogenous grafts were reported and these were usually removed from an extremity after amputation The deliberate refrigeration of skin removed at elective operations for clinical use later on is rare, with only two or three reports made during this century One of these appeared only last year when Brown and McDowell,<sup>12</sup> in their excellent monograph, "Skin Grafting of Burns," covered this subject by these words "In one case a successful full-thickness graft on the neck had been stored in an ice-box for 48 hours, as far as is known, this was the first clinical instance of the use of the procedure One can conjecture all sorts of storage plans and tissue-culture plans for grafts, to be used in war time, but final success has not been attained"

## PERSONAL EXPERIENCE WITH METHOD

On September 9, 1932, I first refrigerated skin clinically as a life-saving procedure at an operation upon an infant to replace a large pigmented hairy nevus of the cheek by a full-thickness graft (Fig 1 A, Table-Case 1)

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\* Read before the American Surgical Association, May 3-4, 1944, Chicago, Ill

TABLE I  
SYNOPSIS OF DATA OF 23 PATIENTS IN WHOM REFRIGERATED SKIN GRAFTS WERE EMPLOYED

Patient No and Age	Condition	Reason for Refrigeration	Time Refrigerated	Thick- ness	Type of Graft	Result	Comment
1 G V 298657 17 mos	Pigmented hairy nevus of cheek	Pt's condition prohibited entire procedure so op divided into 2 stages	4 days	Full-thickness skin	Autogenous	Good take	Life saving procedure cessively hot
2 N T 358106 7 yrs	Pigmented hairy nevus lower forearm post surface extending down to volar surface on each side back of wrist and hand and base of fingers	Pt's condition made immediate application hazardous Op divided into 2 stages	6 days	Full-thickness skin	Autogenous	Good take	Life saving procedure
3 S D 350606 23 yrs	Fracture and lacerated tendons at forearm Original skin graft replaced by pedicle flap	Experimental $\frac{1}{2}$ of graft placed in saline solution $\frac{1}{2}$ of graft placed in trypsin	24 hrs	Split skin	Autogenous	100% takes of both	100% takes despite <i>staph alb non hem strep</i> and diphtheroids cultured before application
4 L Z 400631 29 yrs	3rd deg burns of scalp forehead, ears face, shoulders and hands	At op upon eyelids by another operator skin removed to be applied to scalp when granulations were satisfactory and infection reduced	9 days	Split skin	Autogenous	Partial take	Loss apparently due to strep Extra anesthesia avoided
5 A S 282276 56 yrs	Basal cell epithelioma with some squamous cell involvement, orbital and nasal regions	Under anesthetic for a small op skin removed for granulating surface to be ready later	9 days	Split skin	Autogenous	100% take	At time pt allowed up in chair, graft applied on ward rounds Pt spared an extra anesthetic and operation
6 B S 413479 5 yrs	Pigmented hairy nevus of forehead, eyebrow, eyelids nose and cheek	Excess skin saved for possible subsequent op Oversollicitous parent delayed permission	5 mos and 2 days	Split skin	Autogenous	Failure	Apparent take for 10 days but 'melted', disappearing by 18th day Acted like homograft
7 G V 423365 12 yrs	Dermatitis actinica, infra orbital region and cheek	Shorter subsequent op and hospitalization by early removal of skin	10 wks and 3 days	Split skin	Autogenous	Failure	Failure due to long refrigeration <i>Staph alb</i> and <i>hem staph aur</i> present
		Experimental To avoid excision of pt's skin	6 wks & 2 days	Split skin	Homogenous	Failure	Area same as above Refrigerated homografts showed very early dissolution
		Experimental To avoid excision of pt's skin	15 wks & 6 days	Split-skin	Homogenous	Failure	
8 J D 436135 69 yrs	Basal squamous cell epithelioma and dermatitis actinica of nose	Shorter subsequent op and hospitalization Parts of graft placed under forehead flap for future lining of nose, remainder subsequently covered forehead defect	11 days	Full-thickness skin	Autogenous	Excellent take	Donor site healed and pt walking before and soon after 2nd op when graft applied

9 M McL 441436 4 yrs	Pigmented hairy mole, leg and thigh. Grafts from pt and each parent applied 45 days before. Parents grafts failed.	Experimental homografts to grow	Attempt to get at 1st op under forehead flap at short op used later. Saved time of long subsequent operation.	7 days	Split skin	Homogenous	Failure	Further a graft refrigerated 7 days in pt's serum and cells "Melted by 12th day"
10 P P 473765 48 yrs	Basal cell epithelioma of nose and cheek.	Portion of full-thickness graft used at 1st op under forehead flap at short op used later. Saved time of long subsequent operation.	Pt's condition too precarious to allow immediate grafting	11 days	Full-thickness skin	Autogenous	Good take	Donor site healed and pt walking before and soon after 2nd op when graft applied
11 M P 519132 45 yrs	3rd deg flesh burns of face, head, hands and wrist.	Experimental		15 days	Split skin	Autogenous	Slight take only	Bed infected with <i>hem strep</i> , <i>hem staph aureus non-hem staph</i> and diphtheroids
12 J G 507453 27 yrs	Hindenburg disaster. Foreign bodies (tattoo) in right upper arm and forearm.	(a) Part in Ringer's solution at 4° C (b) Part in Ringer's solution "quick frozen" at -72° C, with carbon dioxide and butyl alcohol (c) Part in Ringer's solution "quick frozen" at -72° C, and lyophilized (d) Fresh grafts applied immediately as control		17 days	Split skin	Autogenous	Divided grafts averaged (a) 45% (b) 40% (c) 80% (d) 98%	All grafts divided and distributed over 4 recipient areas. No grafts refrigerated took as well as fresh control. Parts of lyophilized graft took far better than those otherwise refrigerated.
13 E O 698390 22 yrs	Burns mostly 3rd deg, both legs and thighs.	Pt's condition did not warrant further procedures at this op. 3 1-3 dermatome drums of fresh grafts applied, 2 2-3 drums refrigerated and applied at later op when further fresh grafts were also removed and applied.		26 days	Split skin 0.012	Autogenous	Failure	Considerable amount of graft had "melted" by 7th day. Acted like a homograft. Refrigerated too long.
14 W D 705301 47 yrs	45% 3rd deg and some 2nd deg burns, trunk and lower extremities. Pt had pink plasma	Pt's condition. Also to await good granulations		11 days	Split skin 0.008	Autogenous	Almost 100%	
				18 days	Split-skin 0.008	Autogenous	Almost 100%	
				4 days	Split-skin 0.008	Autogenous	Almost 100%	Taken on phlofilm
				18 days	Split-skin 0.010	Autogenous	Almost 100%	Taken on phlofilm
				52 days	Split-skin 0.010	Autogenous	Failure	Taken on phlofilm. Bed excellent, but refrigerated too long.
15 J O'L 714253 7 yrs	3rd deg burns entire left leg, right leg below knee, entire back and left chest, and part of left arm.	Pt's condition too critical to allow immediate application of grafts		10 days	Split-skin 0.012	Autogenous	Good take	Grafts applied at time of further removal of skin.
				3 days	Split-skin 0.008	Autogenous	Calf 60% Back 40%	Recipient area infected. Pt on back and active.

TABLE I—(Continued)

SYNOPSIS OF DATA OF 23 PATIENTS IN WHOM REFRIGERATED SKIN GRAFTS WERE EMPLOYED

Patient No and Age	Condition	Reason for Refrigeration	Time Refrigerated	Thick- ness	Type of Graft	Result	Comment
16 B S 720275 7 yrs	34% 3rd deg burns legs trunk and right upper extremity	To reduce anesthesia time 1 of the 3 derm drums cut was applied immediately, but pt's condition did not warrant further procedures	4 days	Split skin 0 008	Autogenous	100%	Simple staging of procedures per- mitted, possible to stop op at suitable intervals without wasting skin
17 S P 713614 25 yrs	Traumatic amputation of fingers and thumb of hand Pedicle flap abdomen to thumb	To obviate op when necrotic area became covered with granulations	7 days	Split skin 0 008	Autogenous	100%	Graft taken on phlofilm
18 J N 499757 9 yrs	60% 3rd deg burn entire girdle from chest to knees and part of arms	To reduce fluid loss by covering granulations on area not being epithelized by pt as 250 sq in unrefrigerated homograft from father melted away	7 days	Split skin	Autogenous	Almost 100%	Saving of pt's life by 8 derma- tome drums fresh homografts was continued by interval application of refrigerated autografts
19 M F 731464 38 yrs	3rd deg burn of left axilla, arm and forearm	To save graft and prevent shock by deferring further debridement and grafting after such treatment with one graft caused massive hemor- rhage from blood dyscrasia	11 days	Split-skin	Autogenous	Almost 100%	Refrigeration made possible saving remainder of graft when un- expected hemorrhage occurred
20 O McD 717603 10 yrs	Extensive 2nd and 3rd deg burns of trunk and both arms	To prevent shock Pt's condition too poor to tolerate further anes- thesia or debridement	6 days	Split skin 0 010	Autogenous	99% take	Approximately 25% loss on arm due to infection
21 J H 737446 26 yrs	45% 3rd deg burns arms, back, sides thighs lower legs, 10% 2nd deg burns arms and shoul- ders	Eschar partially excised, areas not suitable for grafting until later	7 days	Split skin 0 008	Autogenous	100%	Taken on phlofilm as postage stamp grafts to legs spreading over entire area
22 F R 710320 68 yrs	Avulsion of skin of leg	At leg amputation skin salvaged for application to stump surface when condition suitable	2 days	Split-skin 0 008	Homogenous	Temporary 80% take	Taken on phlofilm These homo- grafts 'melted' considerably be- fore fresh homografts applied im- mediately from same donor
23 J P 686474 55 yrs	Amputation of feet at tarso- metatarsal joints	To avoid extra op otherwise re- quired when necrotic area was replaced by granulations	13 days	Split skin 0 008	Homogenous	Temporary 80% take	Early loss due either to inter- vening <i>pyocyanous</i> infection or to allergic sensitivity caused by first homografts
22 F R 710320 68 yrs	Avulsion of skin of leg	At leg amputation skin salvaged for application to stump surface when condition suitable	16 days	Split skin	Autogenous	Failure	1 3 appeared to take but was later destroyed, apparently by infection
23 J P 686474 55 yrs	Amputation of feet at tarso- metatarsal joints	To avoid extra op otherwise re- quired when necrotic area was replaced by granulations	21 days	Split skin 0 008	Autogenous	50% take	Bed unsatisfactory, Infection Graft removed on phlofilm used as small strips, only larger strips persisted

It was an excessively hot day and her condition became so precarious, after removal of the skin and closure of the defect, as to necessitate termination of the operation at this point. The skin was refrigerated and, at a second operation four days later the nevus was excised and the refrigerated skin was applied without hazard and with good result (Fig 1 B).

On January 4, 1935, before the Section on Surgery of the New York Academy of Medicine, I reported nine cases in which I had used this method. Up to the present time we have had a total of 23 patients upon whom refrigerated skin grafts have been applied on 36 occasions. Four of the grafts were

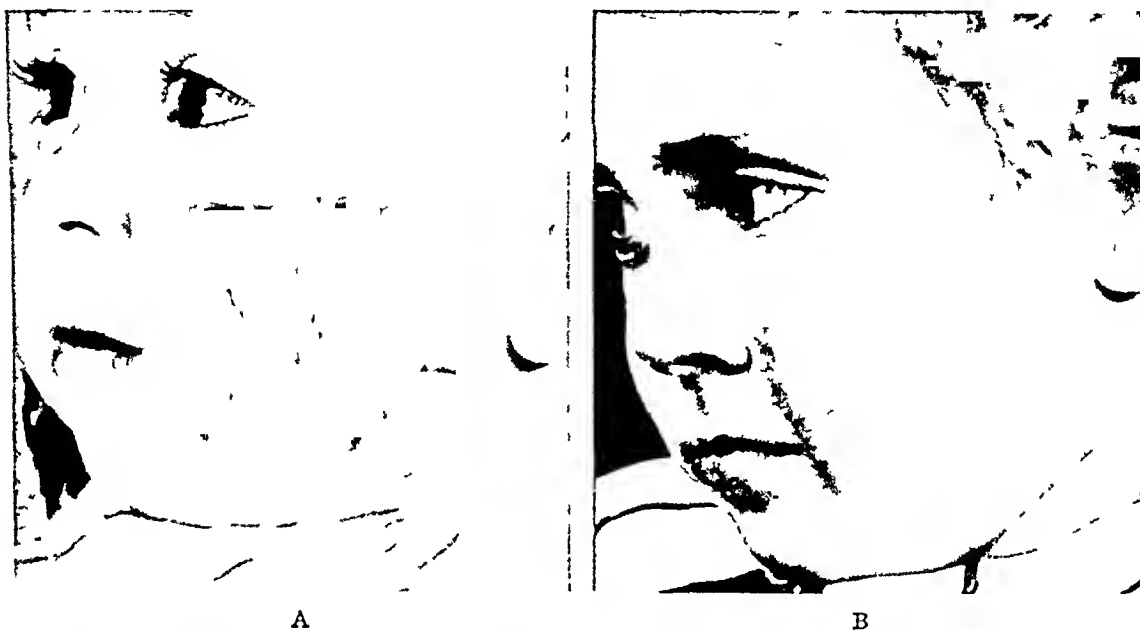


Fig 1—Case 1 (Table). Skin refrigerated and operation terminated because of precarious condition of patient. Skin applied four days later.  
A Condition before operation.  
B Condition three years after operation.

full-thickness skin and the remainder split-thickness. All of the grafts transplanted were autogenous except five which were homogenous, with small expectation of permanent survival (Fig 7). Most of the autografts were transplanted after refrigeration of less than 21 days and these were largely successful, failures being explained on the basis of infection or other unsatisfactory conditions of the beds. In four instances autogenous skin grafts were applied after periods of refrigeration lasting from 26 days to five months and two days (Fig 6). All of these autografts, refrigerated over three weeks, "melted away" as do homogenous skin grafts. Grafts have been applied both on clean wounds and on granulations. No refrigerated skin reported in this series was removed from cadavers, in one instance the source was autogenous avulsed skin from an amputated leg. Four of the procedures were purely experimental.

#### TECHNIC

The technic of skin refrigeration is simple. It is often advantageous to use film-cemented grafts. These are obtained by cementing sheets of phlofilm,



or other similar film, over the drum of the Padgett dermatome, applying rubber cement to this covering film as well as to the skin, and cutting the grafts in the usual way. This technic has been reported from my clinic within the past month<sup>13, 14</sup>. It is not necessary, however, to remove the grafts on film.

In either case, the grafts are folded together (Fig 2), so that the raw surfaces are in contact, thus preventing excessive evaporation. The epithelial

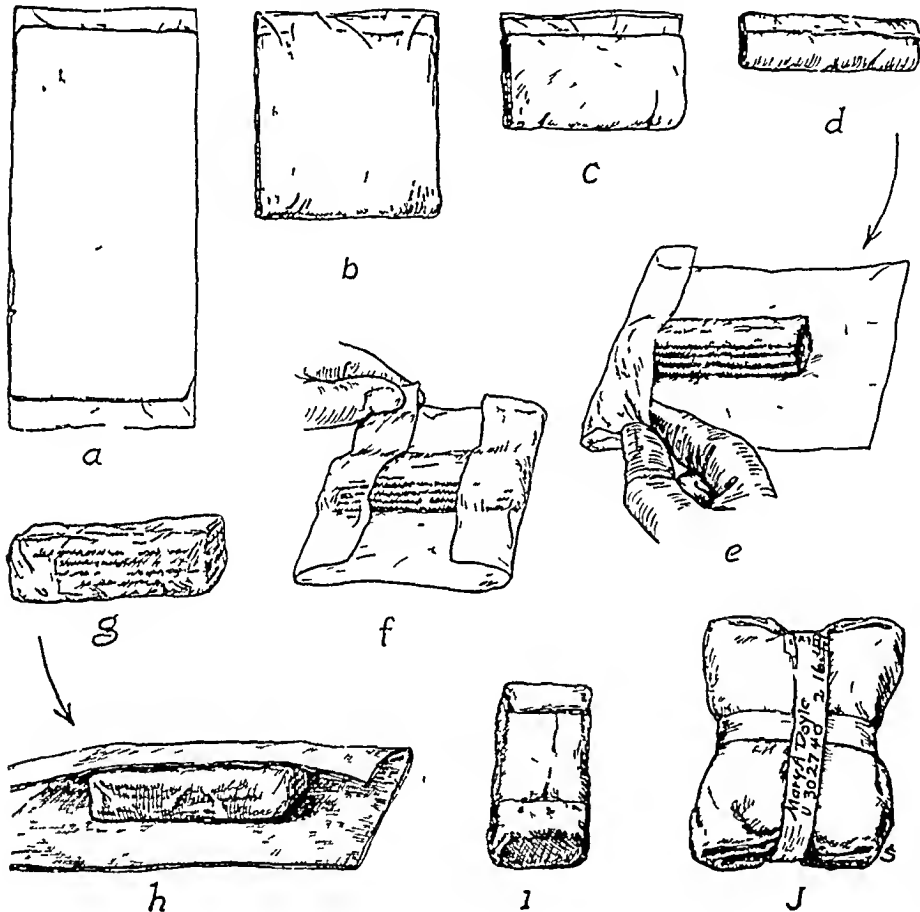


FIG. 2.—Method of preparing graft for refrigeration  
A. Film cemented graft  
B, C, D. Folding of graft on itself, raw surface to raw surface  
E, F, G. Wrapping grafts in a sheet of film  
H, I. Wrapping grafts in xeroform or vaselined gauze  
J. Packet wrapped in two sterile towels

covering, especially with the overlying adherent phofilm, tends to prevent this evaporation. The folded grafts are then wrapped in additional film, and this packet is subsequently wrapped in several layers of xeroform or vaseline gauze of a fine mesh in order to further seal the grafts to prevent them from drying. This package is wrapped in two sterile towels and marked with the patient's name and date to identify it. The bundle is refrigerated in the ice-box at approximately 4° C, the ordinary refrigerator being satisfactory. When the grafts are desired for application, the outer towel is

removed and the grafts are treated and applied in the same manner as fresh grafts

### LYOPHILIZED SKIN GRAFT

At this time I wish to make a preliminary report of one case in which quick-freezing of skin grafts was used and one of the grafts was lyophilized<sup>15, 16</sup> as well. This was the case of a tattooed man (Fig 3, Table-Case 12) who desired removal of his self-made decorations. At the first operation three



FIG 3—Case 12 (Table) Skin grafts refrigerated 17 days (a) at 4° C, (b) quick frozen at -72° C, (c) quick frozen and lyophilized  
A Tattoo marks right arm After excision areas grafted with refrigerated skin

tattoo marks on the left arm were removed (Fig 3 E), as were split-thickness skin grafts from the entire right thigh. Some of these grafts were applied to the denuded areas on the left arm and the remaining grafts were treated in three different ways. One graft was placed in Ringer's solution and kept at approximately 4° C, another graft, also in Ringer's solution, was frozen with carbon dioxide snow and butyl alcohol at -72° C, and was kept frozen, while the third graft was frozen in the same way, but, in addition, was lyophilized by means of a vacuum. This caused it to become shrunken, hard, and apparently dry.

LOCATION As applied

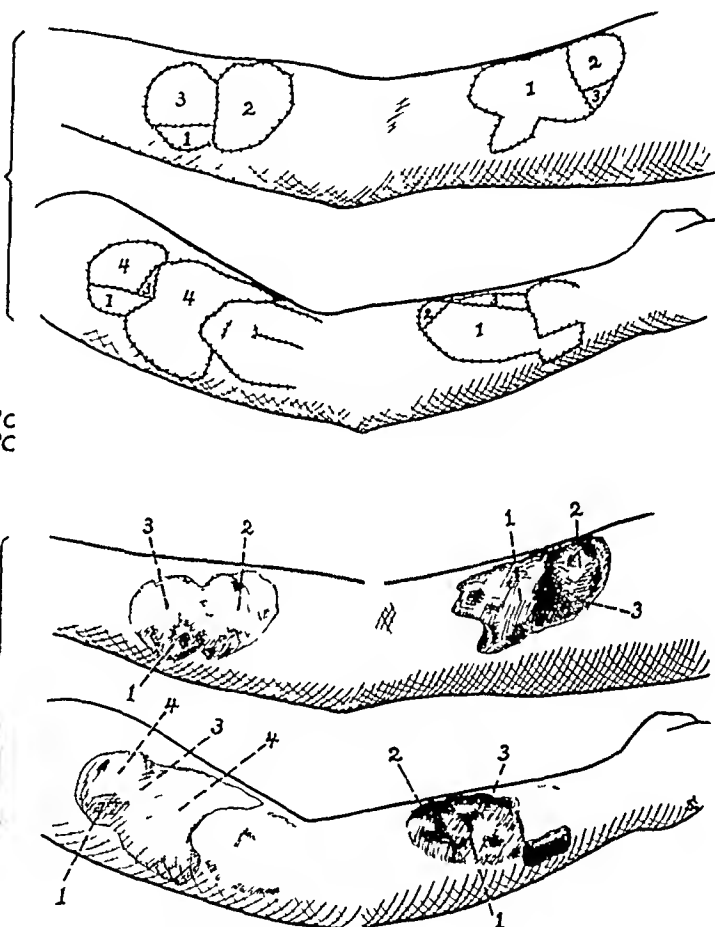
April 19 1938

- \* 1 17 days old  
\* 2 " " "  
\* 3 " " "  
\* 4 Immediate

GRAFT How treated

- \*1 In Ringer's @ 4°C  
\*2 " " frozen @ -72°C  
\*3 " " " " -72°C  
\*4 Fresh and lyophilized

CONDITION May 13 1938  
21 days after application



The fresh control graft resulted in about 98 per cent take. There was considerable loss in all the refrigerated grafts (Fig 3 B [lower], C and D), some parts of the graft placed in Ringer's solution at 4° C and also of that frozen at -72° C were largely lost. Portions of the divided lyophilized graft averaged approximately 80 per cent takes and were definitely better than portions of the other refrigerated grafts. There is no question of fact that this skin graft, which was frozen at -72° C and dried by the lyophilizing process, actually survived this treatment and persisted as living skin, although it was a less satisfactory transplant than the control fresh graft that was immediately transplanted. Modifications of this technic are now being tried to determine if lyophilized skin grafts can be transplanted more successfully.

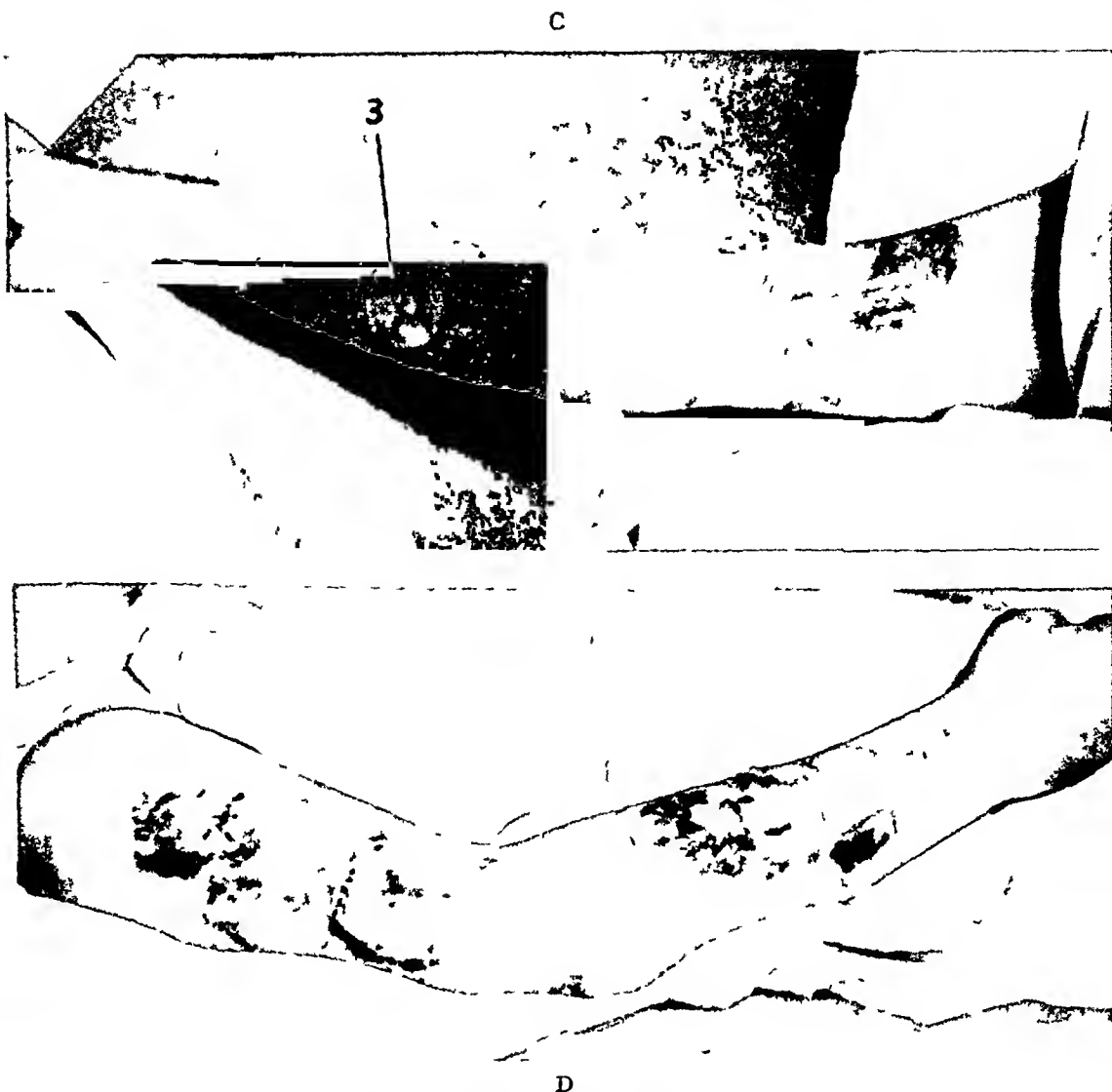


FIG 3—C, D Condition 18 days after grafts applied. Note especially area No 3 on lower forearm where lyophilized skin graft remained strong



E, F—Condition six months after refrigerated grafts applied

and after longer refrigeration. Such an attainment would hold valuable possibilities.

#### CASES AND INDICATIONS FOR USE

There are several indications for the use of refrigerated skin grafts. If an excess of skin is left over after an operation this may be refrigerated for future use, should the original grafted skin not be completely successful.



FIG 4—Case 2 (Table). Operation to graft full thickness skin to replace pigmented hairy nevus of forearm, wrist, and fingers divided into two stage operation as life saving measure. Original operation terminated when condition became critical after excision of full thickness skin and split skin grafting of donor site. Skin refrigerated and at second operation, six days later, nevus excised and area grafted.

A Pigmented hairy nevus before excision at age of seven

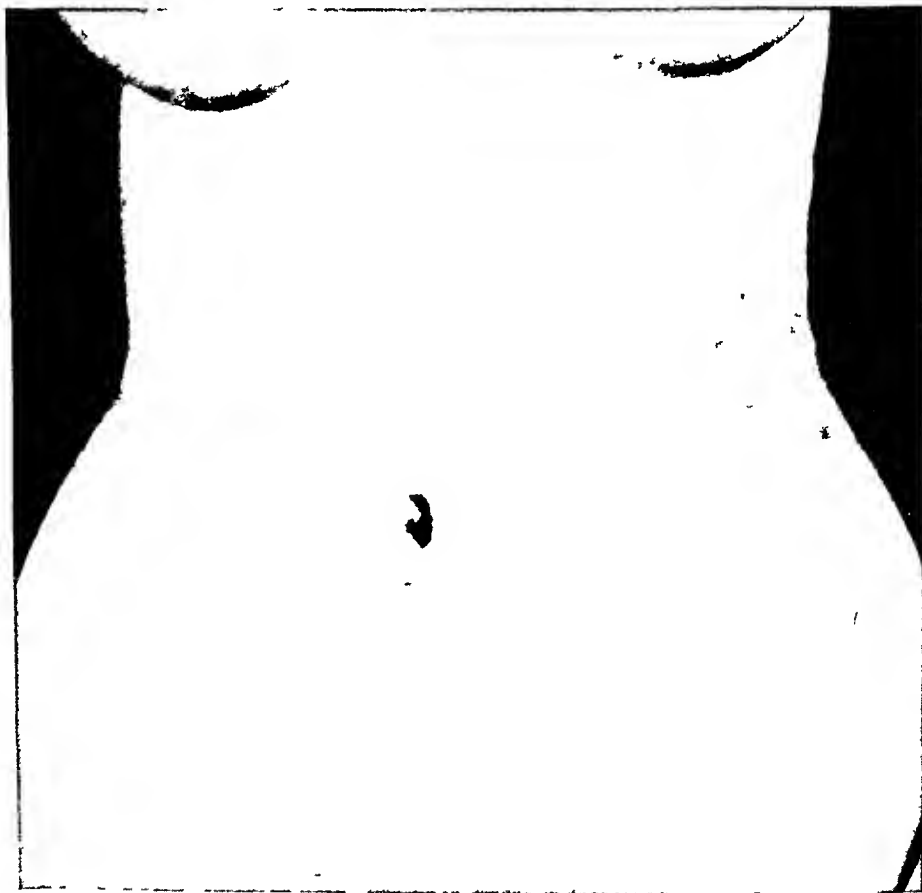
B Refrigerated full thickness skin grafts on forearm and hand applied 12 years previously after six days of refrigeration

On another Service at the Presbyterian Hospital, a graft was removed from the thigh to be placed on granulations on the eyelid and forehead of a burned patient. Since more skin was removed than was needed, the excess was replaced on the thigh. The graft originally transplanted failed to take and a further graft had to be removed. Had the excess skin been preserved and refrigerated, the patient would not have required the second operation, thus eliminating additional anesthesia and longer hospitalization.

Refrigerated skin may be removed at a minor operation (Fig 5) when it is known that skin will be needed subsequently and this may be applied on granulations without an anesthetic or on clean wounds under anesthesia if required.

In burned patients (Fig 9) the grafts may be removed and refrigerated at the time that the eschar or slough is cut away, especially if the patient's condition does not warrant application of the grafts in whole or in part at the time of débridement. As the granulations become satisfactory for grafting the refrigerated grafts may be applied.

A portion of the skin may be used at the first operation and the remainder applied at a later date (Fig 8). The donor site may by this time be



C

C Donor site on abdomen and chest 12 years later

completely healed and the patient ambulatory, thus he can leave the hospital earlier than if the graft were freshly removed at the time of application.

Avulsed skin from a crushed extremity may be removed and refrigerated and kept until satisfactory granulations have been produced and the threat of gas gangrene or other serious infection has been eliminated.

On certain occasions refrigeration of skin may be a life-saving method (Figs 1 and 4), in that it permits dividing a long, hazardous operation into two less taxing stages.

#### SUMMARY

Refrigerated skin grafts are seldom used in surgery today, although the technic is simple and its application has widespread uses. It is of special value in grafting young, debilitated, or extensively burned patients.



B

C

FIG 5—Case 5 (Table) Split skin graft, removed under anesthesia given chiefly for minor operation, applied after refrigeration nine days later

A Recurrent periorbital spread of basal cell epithelioma of lower lid requiring radical excision opening into antrum, mouth, nose, frontal sinus and ethmoid cells. On removing specimen cerebrospinal fluid issued from hole in dura. Temporal muscle swung over to plug hole and close openings into all but nasal cavity

B Condition following above procedure showing temporal muscle filling defect and fistula of nose exposing septum. Under anesthesia skin excised and refrigerated and fistula closed by double flaps

C Condition when skin refrigerated nine days was applied without anesthesia at ward rounds



D

E

D Condition one year after applying skin with 100% take

E Condition six years later. Note adjustment of mouth and cheek by tubed pedicle flap from neck to build up cheek for wearing ground glass lens with side shield on spectacles



A



B



C

FIG 6—Case 6 (Table) Excess split skin, not applied when pigmented nevus was excised and grafted, applied five months and two days later with apparent temporary success After ten days graft “melted away” like a homograft

A Condition before operation

B Condition three months after excision of nevus with grafting of split skin Two months later at second operation scar of lower lid excised and area grafted with skin refrigerated five months and two days

C Condition one year after applying refrigerated skin Subsequently postauricular skin grafts to lids and “island” scalp graft to eyebrow improved the condition



The source of the grafts may be cadavers, amputated limbs as homografts, or autografts, or the usual donor areas on trunk or limb of the patient himself or of others. Only autogenous skin grafts may be expected to survive permanently.

The procedure has been employed 36 times on 23 patients at this clinic during the past 12 years. All of the grafts lived if the recipient areas were suitable and if the grafts were autogenous and were not refrigerated for more

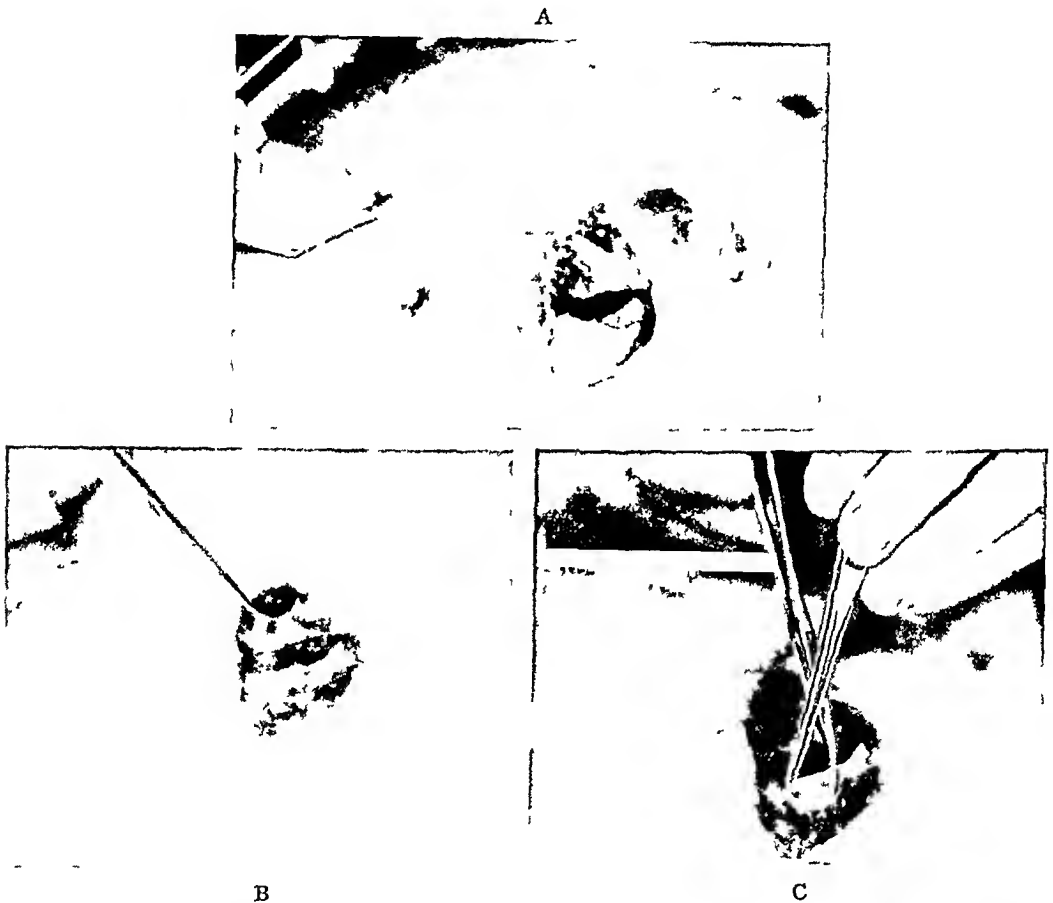


FIG 7—Case 7 (Table). Failure of autograft refrigerated ten weeks and three days and later of two homografts refrigerated six weeks and two days and 15 weeks and six days, respectively, which “melted away” rapidly.

A Condition three days after refrigerated homografts applied. Note successful autograft applied immediately to medial portion. Autograft refrigerated ten weeks and three days had “melted away” on lateral portion before homografts applied.

B Condition on fourth postoperative day—one day later than that seen in A.

C Condition on fifth postoperative day—one day later than that seen in B. Note the transparent pellicle attached only at the periphery.

than three weeks. In our experience those refrigerated over this period failed to survive.

No homograft persisted permanently, although those refrigerated within the three-week period survived longer than those preserved beyond this time.

Lyophilized skin was grafted in one case with partial but definite success after 17 days of refrigeration. This procedure gives promise of being im-



FIG 8—Case 8 (Table) Full thickness graft removed and part buried under forehead flap for future lining of nose. Remainder refrigerated for covering forehead flap defect. Wound was healed and patient was ambulatory before refrigerated skin applied.

A Condition after excision of nose and cheek skin for basal squamous cell epithelioma and dermatitis actinica of nose.

B Condition ten days after skin removed from groin, part placed under forehead pedicle flap and part refrigerated.

C Forehead flap brought down to form nose. Skin, refrigerated eleven days, sutured to forehead defect. Condition ten days after operation.

D Condition three days after division and revision of pedicle flap with partial excision of grafted refrigerated skin on forehead for return of pedicle.

proved and of value With a modified technic it may be possible to graft lyophilized skin with even greater success and beyond the three-week period of refrigeration

#### CONCLUSIONS

The refrigeration of skin should be more widely used (a) to store excess remnants of grafts for possible future use, (b) to delay grafting until suitable conditions of the recipient area prevail, and (c) to divide long hazardous operations into two or more less taxing stages

By this procedure the plan of operations may be facilitated and lives may be saved

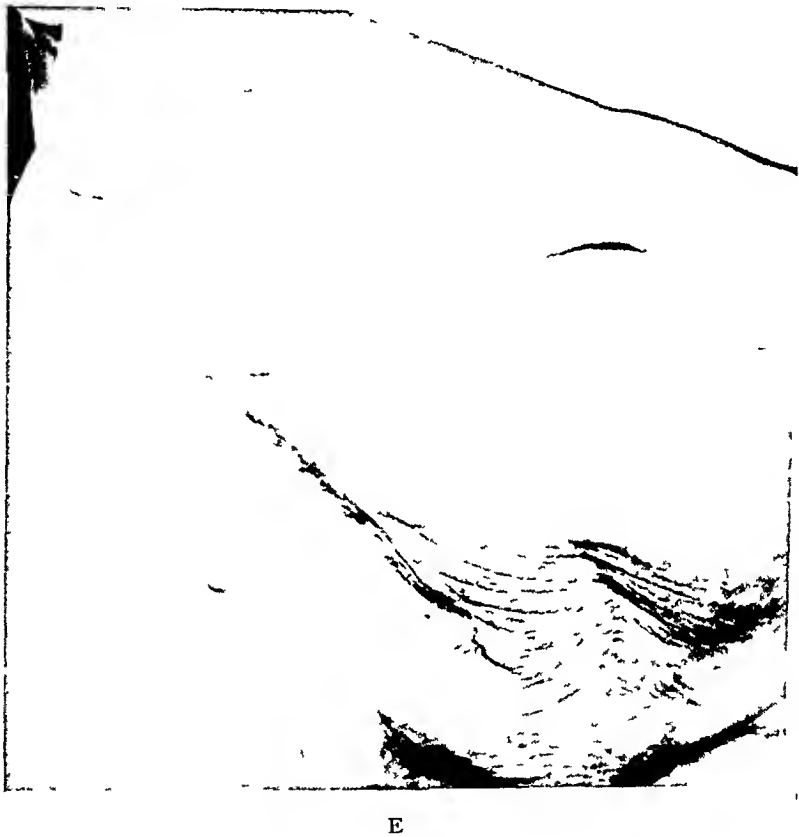


FIG 8—Case 8 (Table) E Donor site on right groin twenty one days after removal of full thickness skin

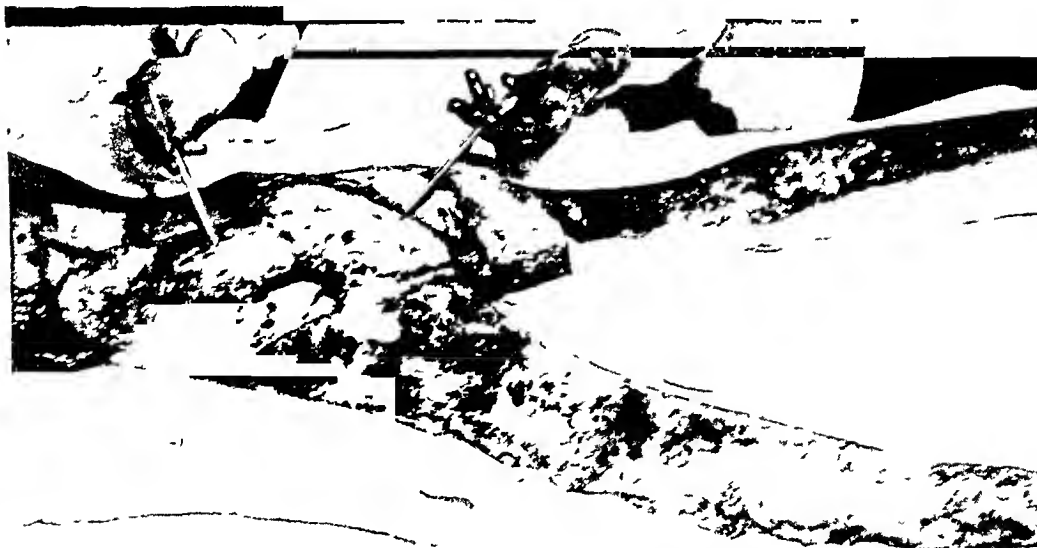
Since this paper went to press Case 23 had film-cemented skin grafts which had been refrigerated 35 days placed on granulating areas where grafts refrigerated 21 days had been lost The 35-day grafts at first were white but subsequently regained their vitality and were definitely covered with epithelium from the grafts themselves as they had been placed on granulations with no adjacent epithelium While these grafts were applied mainly to stimulate epithelium from the patient's surrounding skin with no hope of survival because the refrigeration time had been over three weeks, this is an instance in which successful takes were obtained well over the 21-day limit It is felt, however, that the chance of success is far better if the grafts are not refrigerated over three weeks



A.



B



C

FIG 9—Case 21 (Table) 10% second degree and 45% third degree burns of extremities, back and sides. Value of refrigerating skin to be applied when recipient areas suitable for grafting. Autografts, two drums (64 sq in) refrigerated seven days. Homografts (mother), two drums (64 sq in.) applied immediately, two drums after two days' refrigeration, two drums after thirteen days' refrigeration, five drums (sister) (160 sq in.) applied immediately. [Autografts three-quarters drum (24 sq in) applied immediately and two thirds drum (22 sq in) applied after four days' refrigeration.] All grafts taken on phofilm.

A Condition two months after burn and triple dye applied at another clinic, twenty days after autografts, refrigerated seven days, applied to lower legs (darker squares), five days after homografts (mother) applied immediately on gluteal regions, three days after homografts (mother), refrigerated two days, applied on perineum, gluteal folds and lower leg (lighter areas). Note eschars on thighs partially coming away.

B Condition of lower leg same day as A. Autografts refrigerated seven days (darker squares) twenty days after application, homografts refrigerated two days, three days after application.

C Condition thirty three days after A and B. Fifty three days after autografts refrigerated seven days were applied to both lower legs. They have now coalesced. Fresh homografts (mother) thirty eight days after application (at scissors) still strong with epithelial outgrowth at periphery but showing beginning dissolution, while grafts removed at same time and applied after thirteen days of refrigeration twenty five days ago show more dissolution than the fresh homografts from the same source.

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DISCUSSION —DR JOHN STAIGE DAVIS, Baltimore, Md I have been much interested in Doctor Webster's important and practical paper The idea is generally prevalent that skin grafts of all sorts should be applied either immediately or within a comparatively short time after being cut, and the question as to whether this was necessary has been interesting investigators for many years

In addition to those investigators mentioned by Doctor Webster, Martin, in 1873, carried out a series of experiments on the persistence of vitality of grafts, and he came to the conclusion that cold favored the success of the transplantation, that heat caused a shorter duration of vitality, and that grafts were best preserved in hermetically sealed tubes It should be remembered that these experiments were done before the days of asepsis It is interesting to note also, that the preservation of dried surface skin for subsequent grafting has been tried by Hodgkin, in 1871, and also by Lusk, in 1895, and by others Ljunggren grafted successfully pieces of skin kept in sterile ascitic fluid from two days to three months

Many of these experiments were carried out with iso- or homografts, and, inasmuch, as isografts are only very infrequently permanently successful, even when immediately transferred, these observations must have been made of the apparent early takes and not of the ultimate results

My own interest in the preservation of skin grafts has been of long standing, and I have used refrigerated grafts off and on for many years. I became convinced by experiments early in my career that not only was the immediate application of grafts unnecessary, but that autogenous grafts of all types could be preserved by simple methods and be successfully transplanted.

It was noted in observing the growth of refrigerated small deep grafts, that while the graft would take and the blood supply would become established, it was fully a week or even longer before any new growth of epithelium was observed from the graft margins, and this growth seemed slower than from immediate grafts of similar type.

For practical purposes, it is seldom necessary to preserve grafts for longer than three or four weeks, as after that lapse of time, the wound is usually healed or the patient is in suitable condition to permit the cutting of fresh grafts.

Immediate grafts are always to be preferred, but refrigerated autografts have a definite field of usefulness, and I have found that they can be used with success as long as five weeks after being cut.

Should it ever be made possible by special preliminary preparation, by new advances in blood grouping, or by any other method to use isografts and to obtain consistent permanent results, then the refrigeration of grafts will be of great additional importance. Some surgeons transplant isografts to cover extensive denuded surfaces as a routine early treatment, when autogenous grafts are not available. These grafts which are ordinarily obtained from volunteer donors and used immediately, may also be obtained from amputated limbs or from fresh, disease-free, cadavers and can easily be preserved by refrigeration, and be a useful source of supply when needed. At the present time, grafts used in this way are only advantageous as an excellent dressing.

The practicability of the preservation of skin grafts has not been generally understood, and Doctor Webster has clearly demonstrated the usefulness of the procedure, and has also developed a simple technic of skin graft preservation by refrigeration, which hereafter should be utilized frequently.

# SKIN GRAFT FIXATION BY PLASMA-THROMBIN ADHESION\*

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THE SURVIVAL of a free skin graft depends upon the rapid establishment of an adequate circulation. During the first 12-24 hours after transplantation it is generally believed that there is an osmotic flow of plasma into the graft. Goldman<sup>1</sup> believed that the graft receives its first nourishment from this influx of leukocytes and lymph which he called "the plasmatic circulation." Davis and Traut,<sup>2</sup> from their experiments, also concluded that there is a stage of plasmatic circulation which probably plays an important rôle in the survival of the transplant. The length of time this osmotic circulation operates is probably variable but there is evidence that it is the only means of nutrition for probably the first 24-48 hours. Davis and Traut state that the first new blood vessels are found in skin grafts between 48-60 hours after transfer.

The early vascularization of a skin graft may be delayed or prevented by numerous factors. The graft may be too thick or of too great area for the vascularity of the bed in question. A full-thickness skin graft will rarely take on a granulating surface. Full-thickness grafts when applied to fresh surgical wounds have a higher percentage of take when the graft is from a thin skin area, such as the groin, inner surface of the upper arm, or eyelid. It is also well known that small full-thickness grafts have a higher percentage of take than those of large square area since in the smaller graft the peripheral circulation established is relatively of more importance. In general, the thinner and smaller the graft the higher percentage of success.<sup>3</sup>

The character of the bed is of great importance in free skin graft survival. High percentage of take cannot be expected on an avascular, fibrotic bed. A lower percentage of take is usual on a soft, yielding, irregular surface than on a smooth firm bed.

If the thickness of the graft is not too great for the vascularity of the recipient bed, then the main problem in securing a take is the continuous maintenance of absolute contact of graft and bed so that early vascularization can take place. There are numerous untoward events which can prevent this complete continuous contact. The graft may slip off the recipient area. The graft may be lifted off the bed by bleeding. Infection may cause purulent exudate formation under the graft. On irregular surfaces the graft may be stretched across depressions, the bed may move unless adequately splinted.

In the past, a high percentage of take has been obtained only by careful attention to many details. The thickness of the graft was selected for the particular area. The graft was fixed by suture or dressing so that it could not slip off the bed. Hemostasis was absolute. The graft was perforated to

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\* Read before the American Surgical Association, May 3-4, 1944, Chicago, Ill

allow serum escape    Compression dressings were used to keep the graft firmly in contact with all irregularities of the bed    Joints were splinted to prevent motion of the bed and inlay forms used on parts where splinting was not possible    This method requires patience and time and any method which would secure as high a percentage of take and consume less time would be desirable    Any adjunct to the usual compression-fixation-suture technic of free graft application which would appreciably increase the percentage of take would be welcomed

An attempt to glue free grafts to the bed by the artificial production of fibrin was first reported almost simultaneously by Tidrick and Warner<sup>4</sup> and by us<sup>5</sup>    Shortly afterwards, Cronkite, Lozner and Deaver<sup>6</sup> reported the same method    These reports were all favorable and differed only in their concept of the objective and in some lesser details    Tidrick and Warner used pooled plasma as the source of fibrinogen from which fibrin was formed by the addition of beef thrombin solution    We used the same method    Cronkite, Lozner, and Deaver added thrombin solution to a solution of fibrinogen from the fractionation of human plasma

Tidrick and Warner used fibrin fixation mainly as an adjunct to the usual compression dressing    They did state, however, that in a number of cases grafts had been applied, left entirely open, and protected from trauma by a wire cradle    Cronkite, Lozner and Deaver glued the grafts in place and then applied a pressure dressing    Both these reports consider graft fixation by fibrin as an adjunct to present methods    We originally reported skin graft fixation by plasma-thrombin adhesion as the sole method of fixation without suture, compression dressings, or splinting    We have continued to study the method on its merits alone    In this report we wish to summarize our experience to date

#### MATERIALS

Thrombin was first prepared in 1933 by Mellanby<sup>7</sup>    He demonstrated some of its properties and among these noted that the time required to coagulate plasma is inversely proportional to the amount of thrombase used    Whatever the quantity used, practically all of the thrombase disappears as fibrin is formed    This is important since Lozner, *et al*,<sup>8</sup> showed that parenteral administration of thrombin is very toxic and results in generalized thrombosis

It is nontoxic when used in ordinary amounts as a hemostatic agent in wounds    Seegers,<sup>9</sup> and associates, showed that 1 cc of a 1 per cent solution will clot 1 cc of blood in two seconds    One part of purified dry powdered rabbit thrombin to 60,000 parts of a 0.25 per cent citrated blood results in coagulation in three seconds    Its use as a hemostatic in wounds has been reported without untoward results<sup>10, 11</sup>    Thrombin is now prepared in quantity by some of the biologic firms for clinical investigation and thrombin from these sources was used \*    It is supplied as a sterile powder in rubber-

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\* Supplied us for investigational purposes by Parke, Davis & Company and by Upjohn Co



stoppered ampoules These ampoules contain different amounts of thrombin, varying with the manufacturer The amount of active thrombin is measured in biologic units The most commonly used is the "Iowa" unit This unit is defined as that amount which will clot 1 cc of standard fibrinogen solution in 15 seconds<sup>12</sup> Originally, sterile thrombin powder in ampoules containing 10,000 Iowa units was supplied by one of the biologic firms (Parke, Davis & Co) for investigation This amount seemed greater than needed in most instances and at our suggestion it is now packaged by this firm in 5,000 unit containing ampoules Thrombin has also been given us for trial by another firm (Upjohn) in ampoules containing about 600 Iowa units which is more nearly the amount needed for skin graft fixation

The entire 10,000 units of thrombin can be used by dissolving the contents of an ampoule in 10 cc of saline The ampoule is sterilized by immersion in antiseptic alcohol prior to operation Thrombin solution of this concentration will clot ten times its volume of human blood in three seconds and is a highly effective hemostatic We have found that it is preferable to use a weaker solution than this for skin graft fixation since with concentrated thrombin, fibrin is formed so quickly that adjustment of the graft has to be quite hurried If 250 units of thrombin are dissolved in 10 cc of saline, one part of the resulting thrombin solution when added to four parts of plasma in a test tube produces a fibrin clot in 35 seconds We have divided under sterile conditions the thrombin supplied in ampoules into amounts containing 250 units of activity At first, we did this by dissolving the 10,000 units and then dividing it by volume<sup>5</sup> However, this necessitated refrigeration of the solution and the potency of the solution decreased with time We have found that it is simpler to divide the thrombin by weight and keep a number of small sterile vials containing 250 units on hand in the operating room Following the packaging of thrombin in smaller amounts we have recently been using the entire contents of a 600 unit ampoule dissolved in 10 cc sterile saline with satisfactory results

We have not found it advisable to change our original way of having small amounts of plasma available at all times We package 5 cc of plasma in pyrex tubes sealed with rubber stoppers These are kept frozen in the plasma bank so that a considerable number are always on hand These small amounts of plasma are all that are ordinarily required in applying a graft of considerable size More can be used if needed The small containers prevent waste and reduce cost

Although only autogenous skin grafts take permanently, it seemed to us that since pooled plasma is used parenterally without reaction, that there was no necessity of this material being autogenous We have used pooled plasma from our bank as the source of fibrinogen and we have seen no reaction or adverse effects from its application to wounds

#### METHODS

Any type of free graft may be applied However, for the purposes of

this study we have confined ourselves entirely to split-thickness skin grafts to eliminate as far as possible the factor of differing percentages of take of varying thickness of skin

If the recipient bed is a fresh surgical wound, hemostasis is carefully carried out. In traumatic fresh wounds, dead and devitalized tissue is removed and the accepted principles of wound care followed. If the site to be grafted is a granulating area, it is prepared by frequent change of moist saline dressings. If infection is marked, azochloramid, Dakin's solution or sulfafilm is used locally in preparing the area. The granulations are cut or scraped down to a firm base at operation prior to applying the grafts.

The grafts are cut either free hand or with the dermatome. The bed to receive the graft is flushed with stock plasma. Excess is avoided since the fluid portion remains after fibrin is formed. The grafts are not placed in saline or washed following their removal since this removes the small amount of natural adhesive agents present. (It has been noted before that grafts seem to adhere and take better if this detail is followed)<sup>1a</sup>

The under surface of the graft is wet with thrombin solution. The graft is quickly spread over the bed and then held firmly and smoothly in place for two minutes. This is an important detail since fibrin fixation takes some seconds to occur and following its formation the fluid remaining is extruded. The graft will ordinarily be securely stuck in two minutes. In this series no dressings have been applied to secure compression. In some instances a protective dressing has been used. Joints have at times been splinted and in other instances extremities merely suspended in a cradle.

## RESULTS

We have performed 22 separate free split-thickness skin grafts using fibrin fixation, without pressure dressings or suture. In some instances splinting has been used because the age of the patient was such that cooperation could not be obtained, or as a means to protect the wound from the bed clothes. On extremities where the part could be suspended no dressing whatever has been used. On other parts merely a loose dry gauze for protection has been applied. The amount of skin transferred at one operation has varied from four square inches to 200 square inches. The majority of cases were wounds of considerable dimension usually exceeding 30 square inches.

We have divided these cases into two groups for the purpose of study (1) Those in which the recipient bed was fresh, and (2) grafts placed on granulating surfaces. This division has been made since the percentage of take normally expected on fresh wounds is higher than on granulation tissue.

We have grafted 12 cases of the primary graft type. Of these, eight cases have been free grafts placed on fresh surgical beds as, for example, a skin graft following radical mastectomy. There was no loss in this group. In each case the graft took 100%. The four remaining cases in which the bed was fresh were traumatic contaminated wounds. In these the percentage



A



B



C

FIG 1—A Split thickness grafts applied to fresh surgical wound resulting from excision of sarcoma. The surface was quite irregular. The cord like structure in the lower portion of field is the perineal nerve which was dissected out and stuck back to the tissues with plasma thrombin. The illustration shows mottled appearance of graft 48 hours after operation.

B One week later the grafts are fairly normal uniform color. A few mottled areas still remain. There has been a spotty small loss of about 5 per cent.

C One month after application of grafts. Completely healed. Skin normal appearance.

## SKIN GRAFT FIXATION

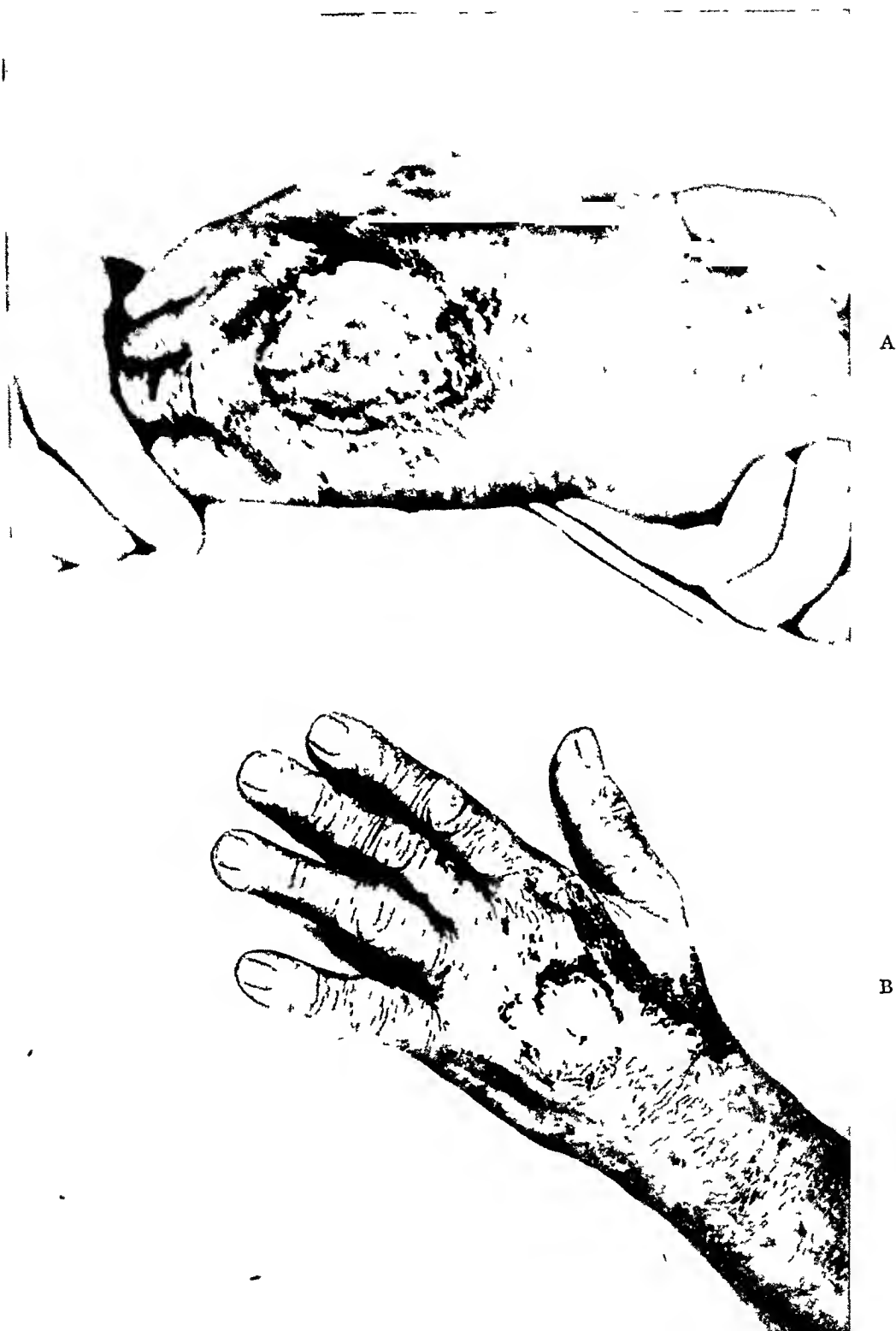


FIG 2—A Immediate application of split graft to avulsion injury after cleansing and debridement. This view taken on third postoperative day shows uniform pinkness of graft.  
B The result four weeks later. There was about a 20 per cent loss due to hematoma formation under graft.

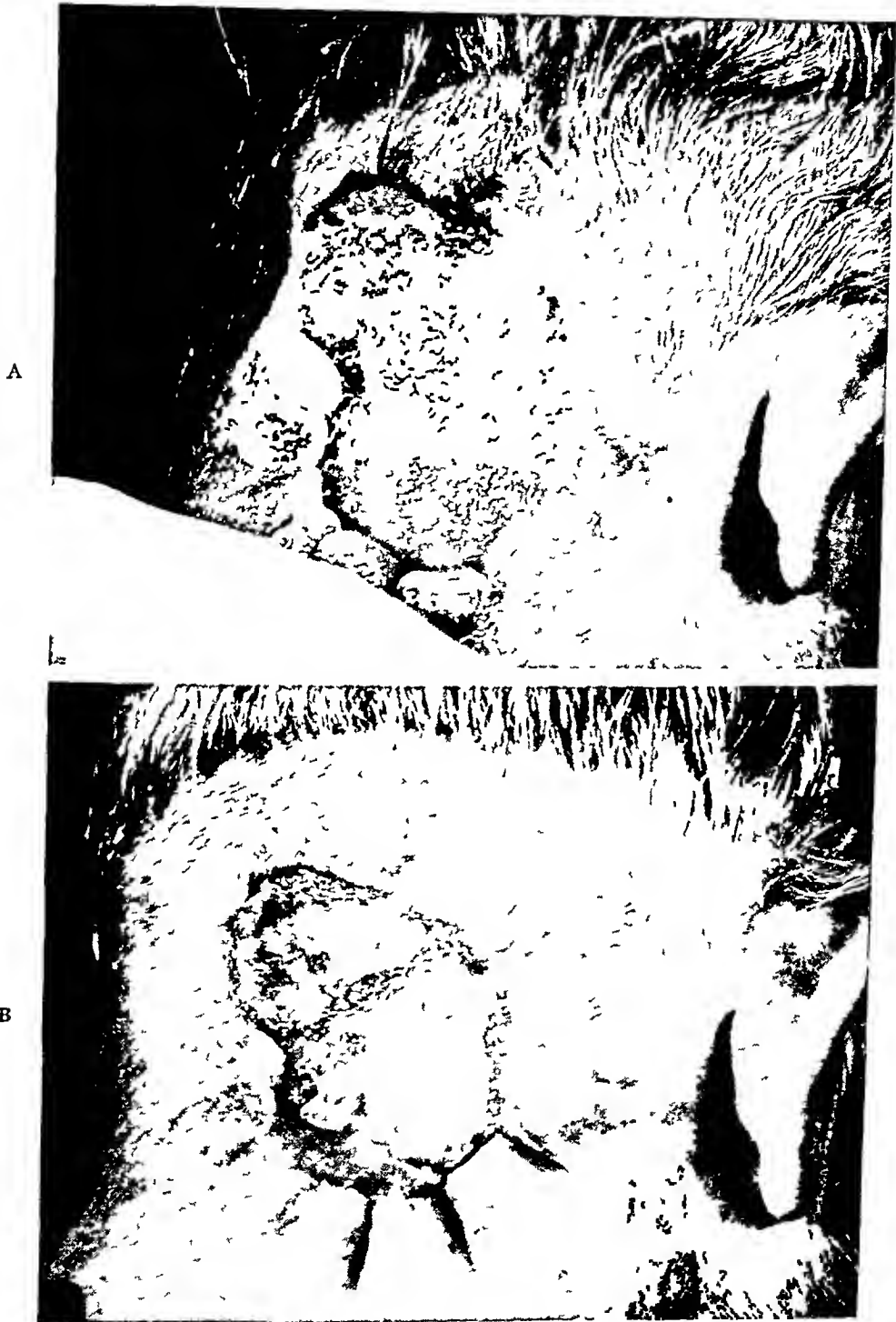


FIG 3—A Granulating wound following excision of carbuncle  
B Split thickness grafts applied directly on the granulating bed took 90 per cent

of take was 48% The figure was lowered by the graft being totally lost in one instance

In the ten granulating wounds a 59% average take was estimated In two instances a graft was lost completely

COMMENT—It is possible that we have been too harsh in the criteria set-up for studying the efficiency of this method of skin graft fixation We have used no sutures to hold the graft in place, no compressive dressing to prevent fluid accumulations under the graft splints have been used in only



FIG 4—A Appearance of grafts applied to contaminated burn wound on third post operative day The mottled areas are pink The major portion is ivory yellow and bullous  
B There was a 95 per cent loss of the graft Loss due to hemolytic streptococcus infection and probably to movement at the elbow

a few instances, nor have we perforated the grafts in all instances to allow escape of fluid accumulation However, in order to judge the value of the method this seemed necessary

An opportunity was afforded for observing the progress of the grafts since they were constantly open to inspection If the graft is taking, the first color changes are observed in about 48 hours (Fig 1A) It may turn a uniform pink at this time indicating a complete take or become a mottled cyanotic color in which case the color may progress to a uniform purplish-pink followed by the pinkness of complete vascularization or areas which are lost may remain a faint lemon-yellow (Fig 1B) In all instances it has been evident that the loss of graft has been due to the accumulation of fluid under it Large bullous areas form which when opened are found in most instances to contain purulent fluid In some of these bullae a gelatinous clot of fibrin is found In the few instances where perforations were made

in the graft, bullae have also formed due to the fact that the perforations are immediately sealed by the fibrin (Fig 4B)

On fresh surgical beds the percentage of take of free skin grafts is ordinarily high and fixation by plasma-thrombin adhesion seems to afford an easy method of obtaining the usual high percentage of take

However, it is our definite impression that the loss of grafts is considerably greater on infected wounds when applied by this method than when compression dressings are used. This applies to contaminated fresh wounds as well as to granulating beds. It is probable that infection is sealed under the graft, drainage is poor and the result is a purulent collection under the graft which prevents vascularization.

It has also been evident that the greatest loss is at points of movement (Fig 1C). The fixation of the graft is firm and of considerable strength within a few moments of application. The fibrin strands, however, do not have great strength and can be rather easily broken by movement. This could be prevented by splinting.

Small size thin grafts, as we have previously mentioned, have a higher expectancy of take than large thick sheets. It has been particularly noted that large sheets of 0.10" to 0.12" thickness have a low percentage of take when applied on granulating surfaces by this method.

Tidrick and Wainer reported a percentage take of 78% when using postage-size split-thickness grafts on granulating areas. This is higher than we have noted and is probably due to the smaller size of the graft since we have used large sheet grafts for the most part. This is further substantiated by the fact that they obtained 73% take with pinch grafts, for the most part applied on less favorable beds.

It would seem to us that the efficacy of the method can not be judged at all when the grafts are first fixed by fibrin and a compression dressing then applied. It is probable that the mere application of the dressing would produce as high a percentage of take alone. It may, however, provide a convenient quick means of holding the grafts in place while the dressing is applied.

#### SUMMARY

The survival of free skin graft depends upon early vascularization. In order for this to occur the transplant must be held in complete continuous contact with the surface on which it is applied.

Fixation of split-thickness grafts on either fresh surgical wounds or granulating beds can be accomplished by the precipitation of fibrin between the graft and the bed by adding thrombin to plasma. The rate of fibrin formation can be adjusted to any speed desired by increasing or decreasing the concentration of the thrombin solution.

The percentage of take has been studied when split-thickness grafts were fixed on fresh and granulating beds by plasma-thrombin adhesion without suture, compression dressing or splinting.

The high, normally expected, take on fresh surgical beds is obtained. On granulating beds the percentage take is lower than normally expected. Large split-thickness sheets take poorly on granulating beds when fibrin fixation is used. Smaller thin grafts have about the average expectancy of take.

We believe that the method is useful in (1) application of grafts on fresh surgical beds, (2) as a method of holding grafts in position while compression dressings are applied, and (3) as a means of applying small grafts, such as pinch grafts, where compression dressings are ordinarily not used.

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DR JOHN STAIGE DAVIS, Baltimore, Md. Before opening the discussion of Doctor Young's very interesting paper, I should like to say that my own personal experience with accelerated fibrin fixation of skin grafts has been very limited.

It has been known for a long time, that shortly after a skin graft is pressed down so that it is in close contact with its new bed, a fibrin network is formed, which seals the graft in place and later by contraction pulls the two raw surfaces into closer approximation. If this does not happen, the graft will fail. Within the last year, a method of accelerating the formation of this fibrin network for the purpose of quickly fixing the graft to its bed has been developed by Doctor Young, and others.

As Doctor Young has stressed, the most important single element in the success of skin grafts is accurate, complete contact and continuous fixation of graft to bed, so that the blood supply can enter the graft as soon as possible without interference. This, he has accomplished by the precipitation of fibrin between the graft and its bed by adding thrombin to plasma, thus hastening the formation of the fibrin network and rapidly fixing the graft.

Possibly the fibrin network thus formed affords better nourishment for the graft,



and possibly the vascularization is quicker following the fixation of a graft with the thrombin-plasma mixture, but it must be borne in mind that the healing of skin grafts and other wounds takes place by a regular process, and that nature, unless hindered, moves with a fairly even speed, whatever help she may be given

Ordinarily skin grafts which are applied either with or without sutures and are immobilized with supporting dressings are seldom observed during the first 48 hours, but when they are observed, if the grafts have adhered and are going to take, they will usually have assumed a purplish-pink color, which is little if any different from the color, at the same period of time, of grafts which have been fixed, by the accelerated fibrin method

It would be an interesting study to check by injection experiments the speed of development of the blood supply to grafts fixed with thrombin-plasma as compared with its development in similar grafts, which have been applied accurately and immobilized with suitable sutures and dressings

It was not so long ago that sutures were not used at all in securing grafts of any type, but the grafts were carefully applied to the wound prepared for them and were pressed down so that every portion of the graft was in close contact with the fresh or granulating surface on which it was put and was so held until the normal fibrin adhesion took place. A dressing supporting the graft was carefully applied, and the part was immobilized to supply physiologic rest until the blood supply was assured. Then the use of a few marginal sutures was started, then many sutures in the margins and through the base, and now the swing is back to no sutures at all but with the addition of a fixing material

One of the most amazing things about the use of the thrombin-plasma fixation process is that the adhesion between graft and bed holds so closely and firmly that, even after a few minutes, there is said to be no necessity of supporting dressings of any kind even on lips and extremities, and that when dressings are used, it is principally for protection of the graft rather than for immobilizing purposes

Even at the risk of sacrificing a little speed in application, which is one of the advantages of the fixation method, my own feeling is that although the fixation method is used, it would be safer to supplement the security of the graft with some strategically placed sutures, and the whole be immobilized with a carefully applied supporting dressing, and that is what I have been doing

As I have said before, my experience with the controlled fibrin fixation method is very limited, and my results, and those of others whom I have happened to observe, have not been as startlingly good or the method as simple as is indicated by Doctor Young, and other investigators. This is probably due to faulty technic, and I have no doubt that with more experience, the procedure will be a useful one in our hands

The fixation method should be particularly helpful in applying either large or small grafts to uneven areas in which it is difficult to use sutures or to apply satisfactory immobilizing dressings

There is considerable difference of opinion as to the great advantage of the thrombin-plasma fixation method over the older methods. I feel however, that new methods of improving the technic of skin grafting, or any other surgical procedure, should be welcomed and tested out in suitable cases. Possibly too much has been claimed for the fixation method and results equally as good can be obtained by procedures which have long been employed, if these methods are used properly. It has been my observation over many years, that skin grafting, although a fairly simple process in the hands of those who know how and when to use it, is more consistently bungled than almost any other surgical procedure. It is to be hoped that the thrombin-plasma method will make for better general results

In closing, I should like to congratulate Doctor Young on his excellent paper. In it, he has simplified the thrombin-plasma method of fixing skin grafts, and has

presented his subject very clearly. There is unquestionably a wide field of usefulness in the procedure, and I expect to use it in suitable cases with a great deal of satisfaction. I wonder whether the method cannot be simplified even to a greater degree?

DR HILGER P JENKINS, Chicago, Ill. There is just one point about the use of plasma in this fibrin fixation procedure which I would like to mention. The fibrinogen content of plasma which has been stored at room temperature for some period of time may be sufficiently lowered so that one may fail to get this excellent fibrin fixation which Doctor Young describes. The results obtained with plasma under such circumstances may not be satisfactory, and to overcome this difficulty I would advise the use of fresh plasma to obtain the best results.

JAMES BARRETT BROWN, LT COL, MC, AUS. We are now in the midst of a very great amount of necessary skin grafting and anything that will make it easier will be gratefully received.

It is interesting that this idea has been derived from observations in the use of tissue culture, and it seems evident that tissue culture investigations may produce many more things of importance in clinical surgery.

As a matter of control we have used several different methods and materials in the fixation of skin grafts, chick-embryo extract, chicken plasma, a chemical company's product for coagulation, plain heat applied to the graft and the area, autogenous and homogenous cell extract and plasma, and just atmospheric pressure applied to the graft.

Capt Cannon and I wanted to know if the wounds themselves might not supply the elements necessary for sufficient fixation for these grafts. Slide shown with six different methods, including two depending on the wound content itself, with results the same in all grafts. All took and survived.

Another slide was shown with nine different control methods used. The best method of fixation was not established, but it was thought that thrombin would perhaps prove best and easiest.

Whenever a plastic surgeon can get out of sewing a graft in place, he usually does so, and has done so for many years. Now, in the Service, with difficult types of wounds and the extensive areas that have to be covered on extremities, we have carried on, with what we have always done, and have called it "snubbing" grafts in place.

We take the grafts off, put them where we want them, and then use fine-mesh roller gauze around them to hold them where they belong. It seems that drying the surface of either the wound or the graft, or both, with an electric blower helps in the fixation. The roller gauze can be either wet or greased according to the type of dressing desired.

Slide shown of huge open wound of lower leg with bones and joint exposed, full of all types of organisms, impossible to get clean. This leg was grafted to close the wounds, so that further definitive work on the bones could be carried out. Large pieces of graft (18 in x 3 in) were spread over the area and snubbed in place without sutures.

Slide shown of a nurse who had all the skin burned off the right forearm and hand. This patient did not respond well to anything, and we were left with the problem of closing her wounds with skin grafts to get her healed. Her entire arm and hand was covered with thick split-grafts, snubbed in place with fine-mesh gauze and cotton mechanics waste pressure dressing. Slide shown of donor site on back completely healed.

This is the type of patient that definitely requires a dressing, and it is possible that pressure has something to do with antiseptics in these wounds that have been open for a long time.

A phosphorus burn of the face was shown as another type of wound that would not respond to the local fixation of graft. In this patient the scar was dense tissue, about 2 cm thick, with tremendous hemorrhage coming out of the entire area. We

electd to put on both eyelids in one operation because of the extensive amount of work that had to be done. We feel that fixation with fibrin or heat would be advantageous, but we could not risk letting this patient move around or move his eyes. In this instance the dressing itself maintains the size and position of defect by stay-sutures from side to side, anchored over a form of cotton mechanics waste accurately fitted into the defect.

One of the advocates of the coagulum fixation of grafts suggested stringing the patient out to the four corners of the bed for five days. This method could never be used in an Army hospital, and few patients would like to be tied to a bed instead of having a dressing in place.

Another type of patient that is important is the one with severe inanition that requires extensive grafting. Slide shown of a patient who had lost over 100 pounds. He had open areas over the sacrum in two areas, both heels and one elbow were exposed. It was thought that one important reason this patient would recover was because of pressure dressings applied over split-grafts which had been snubbed in place. Slide was shown of dressings at time of first change with widespread *B. pyocyaneus* present. This is known not to be a bad infection for a wound, but is a bad one for a skin graft.

Slide showed that *B. pyocyaneus* was everywhere on the dressing except where the graft was and it was felt that the use of the pressure dressing made the growth of this graft possible. There was practically 100 per cent growth of the skin graft in this heavily contaminated field.

Grafts do not necessarily have to be sewed on, they may be snubbed in place with bandages, or they may be fixed in certain wounds with any of several different methods. On an active service, with multiple problems and different types of bases to graft, it is not thought that pressure dressings will be replaced.

# THE INFLUENCE OF SULFONAMIDES ON POSTOPERATIVE COMPLICATIONS\*

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SURGICAL MORTALITY may result from the failure of surgical methods to accomplish their designated purposes or from one of a number of non-surgical conditions which beset the surgical patient during his convalescence, such as postoperative bronchopneumonia, or urinary tract infections

The benefits of sulfonamide therapy have not been evaluated as fully in this group of disorders as in the management of the primary surgical infections such as cellulitis, and peritonitis

The importance of reducing the danger of these conditions lies not only in the lowering of the mortality among the patients now operated upon but also in making possible some extension of the indications for needed surgical procedures especially in the older-age groups

Chemotherapy may also result in certain shifts of emphasis in technic

In order to obtain a more quantitative conception of the influence of the sulfonamides we have reviewed the postoperative complications on Surgical Service B at the Hospital of the University of Pennsylvania for a period of three years prior to the time that the first of the sulfonamides became available to us and for a period of four years after most of these drugs had come into general use The first period extended from July 1, 1933, to July 1, 1936, and the second from July 1, 1939, to July 1, 1943

It was not anticipated that the incidence of these complications would be lowered because the drugs were, in general, used therapeutically and not prophylactically On the contrary, as we came to have better control over some complications a greater number of poor risks were accepted so that the incidence of some of the complications has risen

The pulmonary complications are presented in Table I The most striking change is in the mortality of bronchopneumonia which declined from 69 per cent to 9 per cent without a very marked change in incidence

The other complications had not carried much mortality previously, so that little improvement could be expected Pulmonary embolism being a vascular rather than a respiratory complication has not been included

The wound complications, except for disruption, were seldom a cause of mortality The mortality after disruption in the past has generally been

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high An extensive review of the subject by Sokolov<sup>1</sup> gives a figure of 32 per cent for mortality Eliason and McLaughlin<sup>2</sup> reported 25 per cent from this hospital in 1934 It is of interest that only one of the disruptions of abdominal wounds in the sulfonamide period died

The other complications have been divided among infections of the urinary tract, the salivary glands, thrombophlebitis and miscellaneous infections In general, little mortality resulted in the first period from the urinary tract complications but they were often extremely prolonged and refractory to treatment before the sulfonamides were available At present they seldom fail to respond promptly to chemotherapy and although they may recur they no longer constitute the problem which they did formerly

TABLE I  
POSTOPERATIVE RESPIRATORY COMPLICATIONS  
*Service B—Hospital of the University of Pennsylvania*

Year	Atelectasis		Broncho-pneumonia*		Lobar Pneumonia		Pleural Effusion		Bronchitis and Upper Respiratory Tract Infection	
	Lived	Died	Lived	Died	Lived	Died	Lived	Died	Lived	Died
1933-34	1		1	4					4	
1934-35			2				1		4	1
1935-36	1		1	5					8	
	—		—	—			—		—	—
1933-36 Totals	2		4	9			1		16	1
1939-40			2	1			2		3	
1940-41	4		2			1	1		6	
1941-42	3		6		1				3	
1942-43	4	1	9	1			1		—	—
	—	—	—	—	—	—	—	—	—	—
1939-43 Totals	11	1	19	2	1	1	4		12	

\* Bronchopneumonia mortality

(1933-39) Before sulfonamides were available—13 cases with 9 deaths—69 per cent

(1939-43) After sulfonamides were available—21 cases with 2 deaths— 9 per cent

Parotitis and similar infections in the other salivary glands were associated with a fairly high mortality in the past though experience in the cases reviewed is too limited to be of much interest statistically However, we have gained considerable confidence in dealing with this complication and although some of the cases come to external drainage the danger of septicemia is probably reduced It is hoped that penicillin will prove much more effective in this condition than have the sulfonamides Some of these cases have been treated successfully by the roentgenotherapy department of this hospital

The causes of thrombophlebitis are still rather obscure and as most of the mortality resulting from it is due to embolism it is not likely to be reduced by the sulfonamides Actually, the incidence of thrombophlebitis has increased sharply, being over four times as high in the second group as in the first It is not clear from the available statistics whether this is related in any way to the use of sulfonamides or to other factors, such as more frequent recognition The examination of patients for Homan's sign only became routine during recent years

In the miscellaneous group of postoperative complications of an infectious nature, the mortality has remained about 25 per cent. Otitis media and mastoiditis, which formerly occurred from time to time among children who were in the hospital for other operations, is no longer the problem that it used to be. No instance of mastoid involvement has been recorded in the sulfonamide period.

It must be admitted that the free use of the sulfonamide drugs has introduced a new series of complications—the various drug reactions. Such reactions have been recorded 17 times in the four-year period reviewed, an incidence of 0.34 per cent of all cases on the service. None of these reactions resulted in death. The most common reactions were fever, which occurred eight times, and icterus, which occurred eight times. All of the patients developing icterus had received sulfanilamide. In none of the cases that received sulfadiazine alone was it recorded. Skin reactions were noted only twice, and agranulocytosis and severe anemias were not encountered. Cyanosis, and mild to moderate anemia, following sulfanilamide occurred frequently and were not recorded as complications. They have occurred seldom if at all in cases treated with sulfadiazine. No instances of urinary shut down were encountered, but a careful control of urine output, microscopic hematuria and sulfadiazine blood levels were necessary to avoid this complication.

**Discussion**—A decided decrease in the mortality of patients with postoperative complications results not only in a saving of the lives of a certain number of persons undergoing essential operations but it also permits the benefits of surgery to be extended to certain patients presenting slightly less urgent indications. In the past, such patients have frequently been advised against operation for conditions which seriously interfere with their happiness. A concrete example of this is the elderly man with a hernia which cannot be satisfactorily supported by a truss. The major reason for refusing operation in certain of these patients has been the danger of fatal postoperative pulmonary complications. On account of this danger a number of such patients have had to live in a condition in which they were unable to do many of the things they enjoyed, sometimes with considerable discomfort.

It will be chiefly in geriatrics and to a less extent in pediatrics, and in the very sick, that the influence of sulfonamides in reducing the contraindications for surgery will be felt.

Just as the selection of patients for operation is influenced by the possibilities of controlling infectious complications, so the choice of procedure in the operating room is affected. For instance, in our clinic gastro-intestinal anastomoses were formerly carried out with the aid of a three-bladed Eastman clamp. In recent years we have done more and more of these operations without the use of clamps at the site of anastomosis. There is more danger of contamination by this method, but hemostasis is more secure and the

temporary ischemia of the tissue adjacent to the anastomosis is avoided. With the sulfonamides one has greater confidence that infection can be controlled if it should arise, and so it seems preferable to give up the clamp and avail one's self of the advantage of the open method.

In non-operative procedures, too, one finds the sulfonamides are having their influence. Formerly, patients were often subjected to considerable pain and hardship in an effort to avoid catheterization. Now if they do not respond to the usual methods of stimulating micturition we have less hesitancy in catheterizing them. Furthermore, if catheterization must be performed three or four times, the catheter is usually left indwelling. An earlier routine of daily irrigations of the bladder in those cases where indwelling catheters are used, no longer seems necessary and the time and inconvenience which this change saves is considerable. Small doses of sulfonamides by mouth seem to control infection better than the older irrigating solutions.

There is a grave danger that a false sense of security will be gained from reliance on chemotherapy and that the sulfonamides will be used to cover slipshod technic. There should be no more serious error. There are many pathogenic bacteria which are not susceptible to the action of any of the sulfonamides and the aim must always be to reduce the hazards of surgery as far as it is possible to do so by all means and not merely to maintain a reasonably low mortality with a minimum of effort.

In nearly every choice of procedure, however, there are several desirable objectives not all of which can be obtained in equal degree. Therefore, if an old technic sacrifices safety from hemorrhage for the sake of safety from peritonitis, a new agent which greatly reduces the danger from the infectious process quite logically leads one to the adoption of a new technic which provides greater safety from hemorrhage even though it may permit slightly more contamination. There will be many technics preferred in the past, which may no longer be best when considered in conjunction with chemotherapy. Considerable time will of course be required to test the changes.

Preliminary experience with penicillin makes it seem probable that this and perhaps other chemotherapeutic agents will permit still further advances.

#### CONCLUSIONS

The mortality of the postoperative complications of an infectious nature occurring on a general surgical service has been studied and a comparison made of the experience during the three years prior to the introduction of the sulfonamides with the experience during the four years following their general acceptance.

The most important advance occurred in the treatment of postoperative bronchopneumonia, the gross mortality dropping from 69 per cent to 9 per cent.

It is pointed out that better control of postoperative complications not only permits some saving of life but also permits a broader selection of

patients, especially in the older-age groups, for certain operations which are definitely indicated but in which in the past the contraindications have slightly outweighed the indications

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# CHRONIC CONSTRICTIVE PERICARDITIS PARTIAL PERICARDIECTOMY AND EPICARDIOLYSIS IN TWENTY-FOUR CASES\*

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CHRONIC CONSTRICTIVE PERICARDITIS is the term most generally accepted to designate an inflammatory lesion of the pericardium and epicardium in which fibrous adhesions often associated with deposits of calcium and occasionally pockets of encapsulated fluid form on and between these coverings of the heart and in which the inflammatory scar contracts around and onto the heart muscle to such a degree that it interferes with the normal diastolic and systolic functions of the heart and causes impairment of circulation.

The circulatory failure produced by this condition develops slowly and insidiously. It is due primarily to progressive mechanical interference with the action of the heart and not to intrinsic cardiac disease, except in cases of long standing in which some associated myocardial atrophy and degeneration result from the constriction. The primary cardiac fault in this condition is physiologic due to the fact that the dense inflammatory scar encasing the heart muscle prevents the heart from attaining its normal diastolic volume and thereby causes increased intraventricular tension which results in an inflow stasis.

It is generally accepted that ventricular output is proportional to diastolic filling. In constrictive pericarditis diastolic filling is less than normal and decreased stroke volume and minute output of the heart result. It is probable that other factors may contribute to the decreased ventricular output to a less but significant degree. One of these factors may be interference with the systolic contraction of the ventricle. This interference is attributable *not* only to fixation of the scar to the myocardium but also to a progressing degree of myocardial atrophy and degeneration from the limited action as well as from the original infectious process.

The primary infectious process which causes constrictive pericarditis may not be and often is not associated with acute symptoms which indicate that the pericardium has been involved. A considerable interval may intervene between the time of recovery of the patient from the primary acute infectious disease which may have been some pulmonary infection and the occurrence of symptoms indicating that the pericardium has been involved in the infection.

## ETIOLOGY

The etiology of this condition is of considerable interest and importance and there is some difference of opinion concerning the type of infecting

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organism Every effort was made to determine the causative agent in the series of 24 cases on which this paper is based The clinical history of previous infectious diseases and present clinical examinations were considered carefully for etiologic factors and also microscopic examinations and cultures were made of the tissue removed at operation in all cases This study definitely proved that the etiologic agent in five cases (21 per cent) was tuberculosis This type of infection, therefore, should always be considered as a possible cause of the disease

In 19 (79 per cent) of the cases the type of primary infection was unknown Eight of these 19 patients gave a history of one or more previous attacks of some pulmonary infection, such as pneumonia or influenza One gave a history of mumps two weeks preceding the onset of symptoms and one, a history of scarlet fever seven years prior to examination at the Mayo Clinic Nine did not give a history of any infectious process to which the condition could be attributed Of the patients who gave a history of previous infectious process, only one presented any indication that the pericardium had been involved at the time of the infection This patient gave a history of pneumonia at the onset of his illness during which pericardial paracentesis was done, with negative findings

I do not believe it possible, or advisable, to attempt to draw any definite conclusions as to the cause of the disease from this relatively small group of cases but it is of interest to note that in only one of the cases was there a previous history of rheumatic fever and in this instance the pathologic study of the tissue removed at operation revealed that tuberculosis was the etiologic agent

Those cases in which the etiologic factor cannot be determined are of particular clinical importance as there is a greater possibility of error in diagnosis when the etiology is obscure

#### CLINICAL FEATURES AND DIAGNOSIS

The two most common conditions with which constrictive pericarditis is most likely to be confused clinically, are cirrhosis of the liver and congestive heart failure owing to intrinsic cardiac disease In most instances, however, the subjective symptoms of constrictive pericarditis are sufficiently characteristic that, when they are correlated with the physical and laboratory findings, a definite diagnosis can be established

Development of factors which produce the clinical syndrome of constrictive pericarditis is slow but progressive The amount of blood entering the heart and being pumped into the circulation by the heart per beat and per minute gradually decreases This decrease results in low blood and pulse pressure, faint heart sounds, tachycardia, paradoxical pulse and auricular fibrillation The back pressure on the venous circulation results in high venous pressure dilatation of veins, enlargement of the liver and transudation of fluid into the tissues of the body, particularly into the abdomen and pleural cavities, as well as into the tissues of the extremities and face

The number and severity of subjective symptoms increase progressively with the course of the disease, the earliest symptoms are general weakness and fatigue. Dyspnea is noted on exertion and usually is relieved by rest, particularly by lying down. Orthopnea is experienced rarely. Digestive disturbances, such as anorexia, epigastric distress and fullness in the abdomen after meals, usually are not noticed until after the liver is enlarged considerably and probably can be attributed to hepatic damage, for these symptoms seem to be more severe in cases in which the tests of hepatic function reveal a considerable degree of retention of dye. Swelling of the abdomen does not occur early in the course of the disease, however, it may be one of the first symptoms noticed by the patient. When ascites develops, it usually becomes progressively more extensive. Edema of the extremities which may extend to the face and neck usually does not occur until after ascites has been present for some time. When venous congestion has advanced to this degree, the entire venous system usually is dilated markedly. This dilatation is particularly noticeable in the veins of the cervical region. The effects of this condition cause increasing disability which gradually becomes total disability unless surgical relief is obtained.

The laboratory findings in chronic constrictive pericarditis give valuable aid in establishing a definite diagnosis. The venous pressure is elevated above normal. The circulation time of the blood is increased. The tests of hepatic function indicate a varying degree of hepatic damage which depends to some extent on the duration of the disease. In the series of 24 cases reported in this paper, bromsulfalein tests of hepatic function revealed some degree of retention of dye in all cases. In two cases retention of dye was Grade 1 (on a grading basis of 1 to 4), in 17, Grade 2, in four, Grade 3, and in one case Grade 4.

Roentgenologic studies of the heart in cases of constrictive pericarditis usually reveal it to be normal or smaller than normal, occasionally slightly enlarged but never markedly enlarged or segmentally dilated as in congestive heart failure from intrinsic cardiac disease and hypertensive heart disease. The presence of calcareous plaques in the pericardium is noted frequently. This is always suggestive of the possibility of a constricting pericardium but calcium does occur in the pericardium without other findings of constrictive pericarditis. I have had under observation two patients who have calcification of the pericardium, for one and two years, respectively. The venous pressure and circulation time of the blood in these two cases were normal. In the usual case of constrictive pericarditis roentgenoscopic examination reveals diminution of cardiac pulsations.

The electrocardiographic findings, although not pathognomonic, are suggestive. In a previous paper published in 1940, Barnes and I<sup>1</sup> made the following statement on electrocardiographic findings: "The electrocardiographic pattern which is most diagnostic is one in which the QRS complexes are of low voltage (below 5 Mm) and T waves are negative in all the standard leads. If the QRS voltage is low in only one lead that will usually be

observed in lead I. The T waves in the standard leads may be of low voltage though upright, they may be iso-electric or may be inverted in only two leads. The Wolferth precordial lead is characterized by an exaggerated Q wave at the expense of an R wave of diminished amplitude. Similarly the R wave in leads IV R and IV F is disproportionately large as compared to the S wave. The T wave in the Wolferth precordial lead is upright in more than half the cases and it frequently arises from an R-T segment that is slightly elevated. The T wave in lead IV R is negative in about half the cases and it arises frequently from an S-T segment that is slightly depressed. The electrocardiograms change very little after operation in the cases in which the operation is not successful in relieving inflow stasis. In cases in which inflow stasis is relieved by operation the electrocardiogram tends to return to normal after operation though some trace of the original electrocardiographic abnormalities may persist for a long time in spite of the fact that normal cardiac function has been restored." The most important clinical features in my series of 24 cases are shown in Table I. These indicate that the most important clinical manifestations of constrictive pericarditis are increased venous pressure, increased circulation time, enlargement of the liver with impaired function, ascites, faint heart sound and diminished force of pulsations, low blood and pulse pressure and the heart of normal size or not appreciably enlarged.

Inasmuch as chronic constrictive pericarditis is essentially a mechanical condition interfering with the function of the heart, it can only be relieved by surgical removal of this fibrous encasement of the heart muscle.

It is important that the diagnosis be made early and operative treatment instituted as soon as the diagnosis is established because the longer surgical intervention is delayed the more extensive the myocardial degeneration will become and the more destructive the effects of the disease will become on other body tissues, especially the liver. The greater the degree of myocardial atrophy and degeneration the greater the hazard of operation and the less satisfactory the ultimate operative results.

#### SURGICAL TREATMENT

My experience in the surgical treatment of constrictive pericarditis consists of this series of 24 cases in which partial pericardiectomy and epicardiectomy with epicardiolysis were performed. I have used the term "epicardiolysis" to designate the separation of the innermost layer of the pericardium from the heart muscle. This procedure is used in addition to resecting a portion of pericardium and epicardium. Epicardiolysis is an important and essential part of the operative procedure. Nine of these cases were reported by Barnes and me in 1940.

*Preoperative Treatment*—The preoperative preparation of patients who have been selected for surgical treatment is directed at removing the effects of the circulatory failure owing to the constriction of the heart and at improving the function of the structures involved.

The intake of fluid should be limited to from 1,200 to 1,500 cc in 24 hours. Patients should receive a diet high in protein and low in salt. Daily administration of vitamins may be of value in improving the general resistance of the patient. When tests of liver function indicate considerable damage, vitamin B-complex and glucose administered intravenously, or by mouth, may be helpful in improving the function of the liver.

The body cavities and tissues should be relieved of as much excess fluid as possible. When large amounts of fluid are present in the abdominal and pleural cavities, the fluid should be removed by aspiration and periodic use of diuretics should be utilized to relieve edema of the tissue and keep it at a minimum.

The value of preoperative administration of digitalis is questionable. In the first cases digitalis was given before operation but its use before operation did not produce appreciably satisfactory results and has been discontinued except in some cases of auricular fibrillation. I prefer not to have the patient receive digitalis before operation unless its use is definitely indicated because its stimulating effect on the heart muscle may result in a false impression of the ability of the heart to withstand the surgical procedure. I believe that if digitalis is not used preoperatively, a better evaluation can be obtained of the amount of irritation the heart muscle can safely withstand during the operative procedure.

The level of blood urea, plasma chlorides and serum protein and the carbon dioxide combining power of plasma are determined routinely before operation to see that they are within normal limits as well as to have a control for the postoperative determinations. The type of the patient's blood is determined and blood of similar type is held available for intravenous administration at the time of operation if it should become necessary to utilize it because of loss of blood or severe decrease in blood pressure. Blood or other fluids, however, should not be administered intravenously during operation unless their use is indicated specifically.

*Preliminary Medication*—Preliminary medication is begun the night before operation and consists of 15 grains (0.1 Gm) of pentobarbital sodium taken orally. Two hours before the time of operation another dose of 15 grains (0.1 Gm) of pentobarbital sodium is administered by mouth. This dose often is repeated an hour before operation. Thirty to 45 minutes before the time of operation  $\frac{1}{6}$  grain (0.01 Gm) of morphine sulfate and  $\frac{1}{150}$  grain (0.0043 Gm) of atropine sulfate are administered hypodermically. Morphine should be used with caution and in sufficiently small amounts so that it will not interfere with respiratory function. Amounts vary with the age and condition of the patient. I believe that it is advisable to omit its use for children less than 15 years of age.

*Anesthesia*—General anesthesia is advisable because the operation may require considerable time. This time factor is tiring for the patient and if general anesthesia were not employed, the nervous strain would be increased considerably and would interfere with cardiac function. Furthermore, if

respiratory difficulties arise, it is advisable to have the patient under complete control. The anesthetic agent is administered by means of a positive pressure apparatus. In my early cases this administration was effected through a closed mask but I now use an intratracheal tube routinely. This change was not effected because of any serious trouble with a closed mask but I feel that the equation of safety is greater if the intratracheal tube is used. It may be, and probably is, unnecessary in some cases, but I do not believe that its routine use produces any harmful effects and if its use becomes urgent, it may be difficult to introduce the tube and serious consequences may result before it can be introduced. Use of the intratracheal tube makes it possible to maintain adequate oxygenation at all times and under all circumstances because it insures an adequate air-way and mucus or secretions can be easily aspirated through the tube. It is also an added protection against respiratory dysfunction arising from collapse of the lung if the pleura should be inadvertently opened on one or both sides.

I prefer cyclopropane as the anesthetic agent. In my earlier cases cyclopropane was used routinely. At present I use cyclopropane in combination with ether. The reason for this modification has been to lessen the occurrence of cardiac arrhythmia which may be associated with cyclopropane anesthesia.

*Operative Procedure*—The patient is placed in a straight dorsal position, on the operating table.

A U-shaped skin incision is made to approach the pericardium extrapleurally through the left anterior portion of the thoracic wall. This incision begins at about the anterior axillary line at the level of the sixth rib, it extends across the thorax to the sternum, the apex of the curve is in the midportion of the sternum and the upper end of the incision extends as high as the third rib on the anterior axillary line.

The pectoralis major muscle is dissected and is reflected with the skin flap. The costal cartilages of the sixth, fifth, fourth and in some instances of the third ribs on the left side are resected subchondrally and subperiosteally from the sternum together with 3 cm of the corresponding ribs. An intercostal muscle flap is then cut from the left border of the sternum and the intercostal vessels are cut and ligated. The internal mammary vessels are ligated in the upper and lower limits of the wound in the thoracic wall, usually beneath the perichondrium of the third and sixth costal cartilages. After the muscle flap is mobilized, any existing pericardial attachments to the sternum are separated and a portion of the left half of the sternum is resected with the rongeur. In some instances it is not necessary to remove any of the sternum beyond the detachments of the cartilages.

The left pleura may be dissected from the pericardium at this time. The pleura, however, is often adherent particularly when the pericardium is calcified, and openings may be made inadvertently into the pleura during its separation. Any openings, thus occurring in the pleura, are immediately closed with catgut. In cases in which only a little pericardial space is free of pleural attachments and in which the pleura is thin and adherent to the

outer wall of the pericardium, it is not advisable to make a wide separation of the pleura from the pericardium until after dissection of the pericardium from the myocardium has been made because of the danger of opening the pleural cavity at this early stage of the operative procedure. Inadvertent opening of the pleural cavity at this time, however, may result in pulmonary

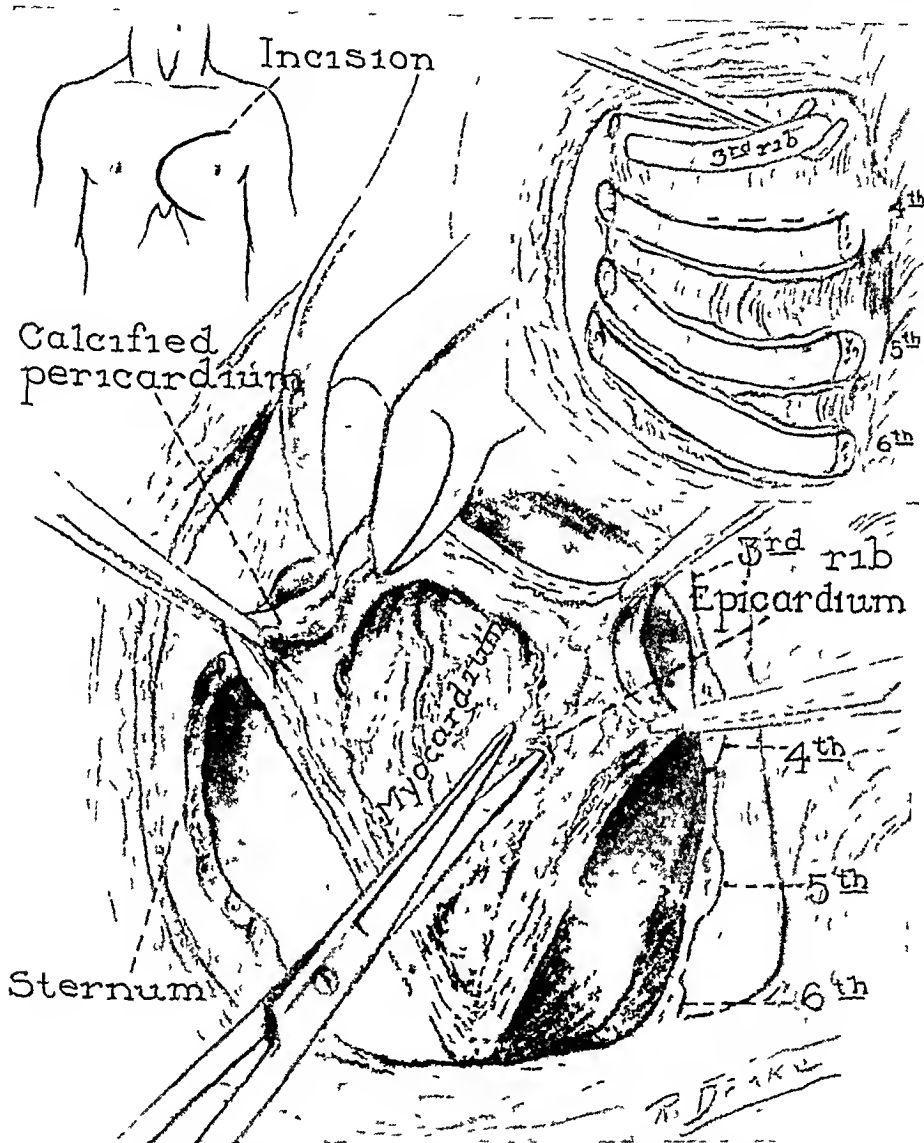


FIG 1—Sharp dissection of the constricting epicardium (epicardiolysis) and pericardium from the myocardium. Bone cutters were required for resection of the scar because of the thickness of the calcification. *Left Inset*: U shaped precordial incision. *Right Inset*: Approach to the pericardium through the wall of the thorax. Resection of the cartilages and 2 cm. of the third, fourth, fifth and sixth ribs on the left side (resection proximal half of sternum).

collapse and respiratory difficulty which may interfere seriously with the patient's progress throughout the rest of the operation. Usually sufficient exposure of the heart can be obtained to complete the dissection of the adherent pericardium from the myocardium without separating the attachment of the left pleura to the pericardium until resection of the pericardium is about to be performed.

The initial incision into the pericardium is important. An attempt is made to make the incision in a region which is removed from the underlying coronary vessels. The site usually selected is close to the sternum or well over the left ventricle in order to avoid injury to the anterior descending portions of the left coronary vessels. The site of election depends to some extent on the type of scar and accessibility of the myocardium. Great care should be exercised to ascertain the actual point of fusion of the pericardial scar and the myocardium before removal of the epicardium is started. The separation of the epicardium from the myocardium is very important and is done in addition to the resection of a portion of the epicardium and pericardium and extends over a much wider area of heart muscle than the area from which the scar is resected (Fig 1). The site of fusion of the epicardium and myocardium often varies greatly, particularly when deposits of calcium are present. In some instances the calcified tissue may extend into the heart muscle and great care is required in removal to avoid serious injury to the heart muscle. During removal of this scar the deposits of calcium should be left attached to the reflected pericardium. In some regions, particularly around the deposits of calcium, the fusion plane is not uniform and the dissection must be carried around the deposit in slightly different planes before it can be removed by sharp dissection. When the calcium invades the heart muscle, no attempt should be made to remove it as the tissue involved may extend entirely through the heart muscle. In instances in which the scar tissue has extended into the heart muscle, small segments of scar should be left attached to the myocardium because of the risk of damaging the muscle or the coronary vessels in their removal. As mentioned previously, in many instances the scar presents irregular lines of cleavage. It often extends into the myocardium at different levels. In these instances it is best not to follow one line of cleavage to the point of injury to the myocardium but to shift into another line of cleavage and then separate the intervening bands to avoid myocardial injury.

An attempt is always made to free the left ventricle first because better function of this chamber of the heart should be established to provide better disposal of the blood before freeing the right side of the heart. In many instances, however, I have separated the greater portion of the right ventricle first without harmful effects.

Opinions differ concerning the amount of pericardial scar that it is necessary to remove as well as concerning the amount of scar to be separated from the heart muscle and from the orifice of the inferior vena cava. I believe it is advisable to separate as much of the pericardial scar as possible from the ventricles, the right auricle and orifice of the inferior vena cava and it is of particular importance to separate the attachment of the right ventricle to the diaphragm. It is of equal importance to separate the apex of the heart and I believe that this should be done early in the operation if possible. Separation of the heart muscle from its fixed attachments to the diaphragm is one of the most important considerations in reestablishing the action of the



heart Improvement in the function of the heart often is noted immediately after the apex and right ventricle have been separated from their fixed attachment to the diaphragm

After the scar has been separated from the heart muscle, the amount of pericardium to be resected depends on the character of the scar and the position and type of fixation of the pleural attachments to the outer wall of

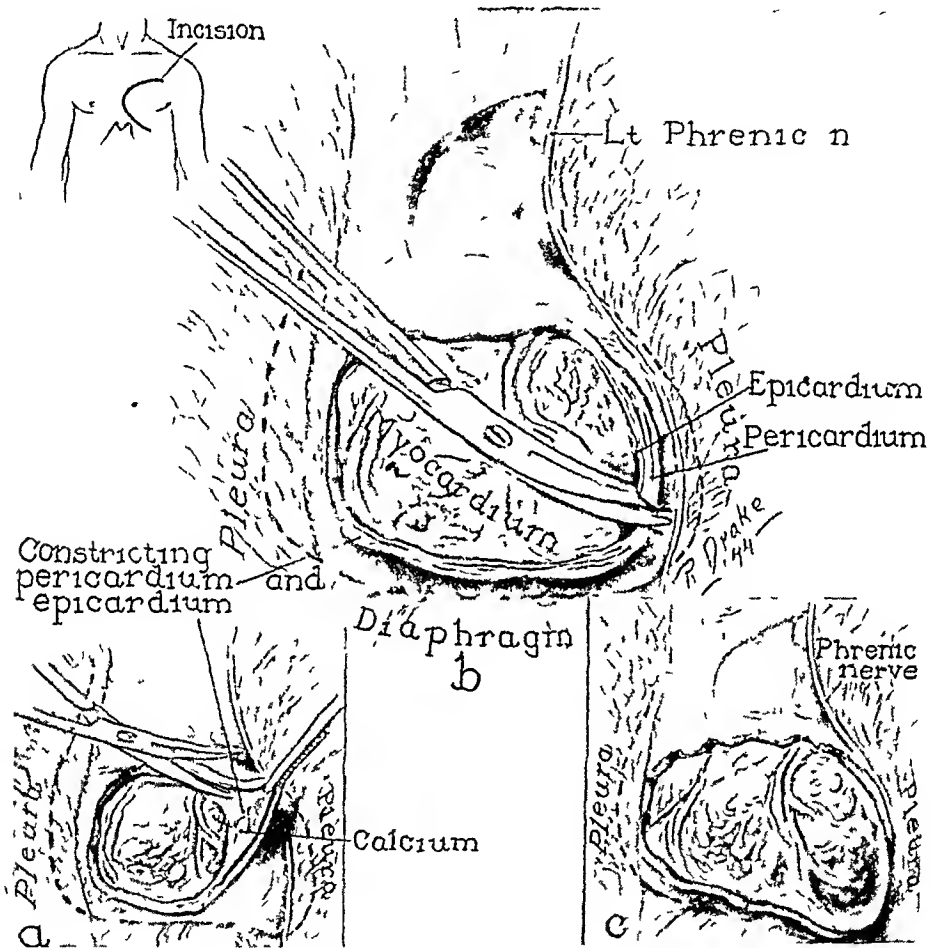


FIG 2—Resection of, and marginal incisions in the pericardium and epicardium after separation from the myocardium *Inset a* Beginning resection of the pericardial scar from the anterior and larger surface of the myocardium *b* and *Inset c* After resection of the pericardial scar, multiple incisions are made into the cut margin of the remaining epicardium and pericardium in order to release the heart more fully, particularly at the apex

the pericardium I believe it is advisable to resect as much of the anterior portion of the pericardium as possible without injuring the pleura By careful dissection the pleural attachments to the pericardium can be separated to approximately the position of the left phrenic nerve and the entire anterior portion of the thickened pericardium extending beneath the sternum is resected If the attachments of the pleura extend high on the pericardium as they often do when calcium is present, it may be impossible to resect an adequate amount of pericardium without injuring the pleura In these

cases linear incisions into the remaining cut edges of the pericardium will produce a much wider opening of the pericardium (Fig 2)

The importance of separating and removing sufficient scar to release the heart cannot be overestimated because, if an adequate amount is not removed, cardiac action will continue to be impaired. This not only will eliminate the possibility of ultimate recovery from the disease but will interfere with the immediate recovery from the operation.

In the course of removal of the pericardial tissue the pulse rate often becomes rapid and irregular owing to the external stimulus to the heart muscle. When the pulse becomes irregular, it is important to cease the operation temporarily. The utilization of frequent rest periods and applications of sponges moistened with warm physiologic solution of sodium chloride will permit the heart to regain or at least partially regain its former rhythm.

The upper half of the wound down to the bed of the cartilage of the fifth rib is closed in two layers. Above the cartilage of the fifth rib the intercostal muscles are sutured to the sternum. The perichondrium of the cartilages of the fifth and sixth ribs is excised completely. From the cartilage of the fifth rib to the lower angle of the wound the subcutaneous tissue and skin only are closed over the heart. Soft rubber tissue drains are placed in the lowermost angle of the wound between the heart and the diaphragm. These drains permit the immediate removal of the serous exudate from the precordial space. The drains are removed from 36 to 48 hours after operation.

A varying amount of serous exudate always follows removal of the adhesions, even though great care is taken to prevent trauma to the tissues as well as to attain accurate hemostasis. If this fluid is permitted to accumulate in the precordial space, it may interfere with the function of the heart which is already laboring under increased stress from the operation. If it is not permitted to drain externally, the fluid may rupture into the pleural space and interfere with respiratory function. When granular deposits of calcium are scattered throughout the pericardium, it is particularly advisable not to have this material drain into the pleural cavity because of the risk of pleural irritation and empyema.

#### POSTOPERATIVE CARE

Immediately after operation all patients are placed in an oxygen tent. The time during which administration of oxygen is continued depends on their progress. This is one of the most important aspects of postoperative treatment, for the oxygen not only prevents cyanosis but aids in relieving stress on the heart. Other postoperative measures are directed toward removal of body fluids and aiding the function of the heart and liver. These measures are similar to those utilized preoperatively for similar purposes. Limitation of the intake of fluid is important, from 1,200 to 1,500 cc of fluid is administered in 24 hours by proctoclysis or by mouth as soon as nausea subsides. The intravenous administration of fluids is avoided if possible. In instances

in which the urinary output is reduced, 10 to 20 per cent solution of glucose may be administered intravenously. This not only aids the urinary output but may benefit the function of the liver. Vitamin B also is given.

TABLE I  
CLINICAL DATA IN TWENTY-FOUR CASES OF CONSTRICTIVE PERICARDITIS

Sex	Duration of Symptoms 3 months to 15 years		Patients	Age of Patients Yrs	Patients
Males			18	1-19	8
Females			6	20-29	6
			—	30-39	7
Total			24	40-49	3
Clinical Features					
Ascites			19	Increased venous pressure	24
Edema of legs			16	(190 to 360 Mm of water)	
Edema of face			6	Increased circulation time	16
Pleural effusion			7	(highest 90 sec with decholin)	
Dyspnea			16	Low blood and pulse pressure	20
Orthopnea			2	Diminished pulsations	24
Cyanosis			3	Auricular fibrillation	4
Weakness			12	Enlarged liver (dye retention)	24
Dilated veins in neck			10	Heart small or normal	18
Gastric distress			8	Heart slightly enlarged	6

TABLE II

NINE CASES OF CHRONIC CONSTRICTIVE PERICARDITIS IN WHICH CURE RESULTED FROM PERICARDIECTOMY

Case	Age		Duration		Venous Pressure, Mm of Water	Etiology (Previous Infections)	Fibrous Adhesions	Results and Time after Operation
	Yrs and Sex		Symptoms	Ascites				
1	27 M		8 yrs	8 mos	310	Unknown (pneumonia 15 yrs ago)	Ca	Cured, 6 yrs
2	38 M		9 yrs	5 yrs	260	Unknown (influenza 11 yrs ago)	Ca	Cured, 5 yrs
3	37 F		1 yr	0	235	Unknown (none)	Ca	Cured 5 yrs
4	21 M		10 mos	10 mos	360	Tuberculosis	Ca	Cured 3 yrs
5	11 M		4 mos	4 mos	280	Unknown (none)	Ca	Cured 2 yrs
6	21 M		6 mos	6 mos	284	Unknown (empyema 7 yrs ago)	Ca	Cured 2 yrs
7	37 F		2 yrs	1 5 yrs	238	Unknown (none)	Ca	Cured 1 yr
8	14 F		2 yrs	2 yrs	315	Unknown (none)	Ca	Cured, 1 yr
9	33 M		3 mos	2 wks	282	Unknown (influenza, 1 yr ago)	Ca	Cured 2 yrs
								Died Auto accident

#### RESULTS FOLLOWING OPERATION IN TWENTY-FOUR CASES

The rapidity and completeness with which recovery occurs after operation for constrictive pericarditis depends on many factors, the most important of which are the amount of myocardial atrophy and degeneration, the amount of hepatic damage, and the thoroughness with which the constricting scar has been removed from the impaired heart. Improvement may be noticed soon after the operation but it proceeds slowly and progressively. Ultimate

complete recovery may not occur for many months. This is somewhat dependent on the duration of the disease before operation. One patient (Case 1) did not obtain complete recovery for nearly two years following the operation.

Of the 24 patients operated upon, 18 recovered from the operation and six died in the hospital following operation. The operative mortality was 25 per cent.

Tables II, III and IV give some of the clinical data and the results of operation in this series of 24 cases. This series includes nine cases (Cases 1, 2, 3, 9, 15, 16, 19, 21 and 22) which were reported in 1940.

TABLE III

NINE CASES OF CHRONIC CONSTRICTIVE PERICARDITIS IN WHICH IMPROVEMENT RESULTED FROM PERICARDIECTOMY

Case	Age, Yrs and Sex		Duration		Venous Pressure, Mm of Water	Etiology (Previous Infections)	Fibrous Ad- hesions	Results, Time after Operation
			Symptoms	Ascites				
10	34	F	2-3 yrs	2 yrs	225	Unknown (none)	x	Marked improve- ment, 2 yrs
11	34	M	2-5 yrs	2 yrs	235	Unknown (influenza, 15 yrs ago)	x	Marked improve- ment, 1 yr 11 mos
12	46	M	3 mos	0	235	Tuberculosis	x	Moderate improve- ment, 1 yr, 1 mo
13	16	M	2 yrs	0	190	Unknown (none)	✓	Progressing im- provement, 5 mos
14	29	F	9 mos	4 mos	204	Unknown (influenza, 1 yr ago)	Calcium Encap- fluid, calcium	Progressing im- provement, 3 mos
15*	43	M	15 yrs	2-5 yrs	315	Unknown (empyema, 15 yrs ago)	✓ Calcium	Improvement (2 operations), 6 yrs 6 mos
16	17	M	3 yrs	2 yrs	340	Tuberculosis	x	Improved, 2 yrs 3 mos. Later died of tuberculous per- itonitis
17	15	M	4 mos	4 mos	255	Unknown (scarlet fever, 7 yrs ago)	x Calcium	Improved, 7 mos Later died of pneumonia
18	17	M	6 mos	3 mos	350	Unknown (influenza, 1 yr ago)	Encap- fluid	Improved, 2 yrs 1 mo. Later died of progressive cardiac failure

\* Pneumonia at onset of illness, pericardial paracentesis gave negative results

Tables II and III give the data on the 18 patients who recovered from operation and include data on four patients who have died subsequently. Table IV gives the data on six patients who died in the hospital following the operation.

Of the 18 patients who recovered from operation, nine (Cases 1, 2, 3, 4, 5, 6, 7, 8 and 9) were cured. By cured, or cure, I mean that they have been able to resume their normal activities with reasonable restrictions. Operation was performed in these nine cases from one year and seven months to six years before this study was made (Table II). One of these patients (Case 9) has died since operation from another cause. After making an excellent recovery and being able to resume his work as a farmer, he was killed in an automobile accident two years and ten months following the

operation The result in one of these cases (Case 4) was especially gratifying as the etiologic agent in this case was tuberculosis This diagnosis was proved by microscopic examination of the pericardium removed at operation This patient is able to carry on his usual activities, and it is now three years and nine months after the operation Of the five patients who had tuberculosis (Cases 4, 12, 16, 19 and 20), this is the only patient who obtained a result

TABLE IV

## DEATHS FOLLOWING PERICARDICTOMY FOR CHRONIC CONSTRICTIVE PERICARDITIS

Case	Age Yrs and Sex	Duration of Symptoms	Etiology (Previous Infections)	Constricting Lesion of Pericardium	Results
19	27 M	1 5 yrs	Tuberculosis*	Fibrous effusion (subacute)	Died 29th day, left tuberculous empyema, multiple pulmonary infarcts
20	26 M	4 yrs	Tuberculosis	Fibrous	Died 13th day, left tuberculous empyema with bronchopneumonia and pulmonary tuberculosis, cardiac failure
21	12 M	5 yrs	Unknown (none)	Fibrous and calcium	Died 4th day, cardiac failure, myocardial degeneration, liver damage, (previous Talma-Morison operation)
22	41 M	4 mos	Unknown (none)	Fibrous and calcium	Died 3rd day, cardiac failure, bronchopneumonia, myocardial degeneration, calcium through wall of ventricle
23	16 F	2 yrs	Unknown (mumps 2 yrs before onset)	Fibrous and calcium	Died 3rd day, multiple bilateral pulmonary embolism
24	12 M	2 mos	Unknown (none)	Fibrous	Died at operation, cardiac failure

\* Previous history of rheumatic fever

that could be considered as a cure In Case 12 the improvement was moderate and in Case 16 the patient died two years and three months after operation from tuberculous peritonitis The remaining two patients (Cases 19 and 20) died in the hospital after the operation

Of the remaining nine patients who recovered from operation (Table III), two patients (Cases 10 and 11) have shown marked improvement two years and one year and eleven months, respectively, following operation One of these patients had received treatment for cirrhosis of the liver for two years Neither of these two patients has been examined in the past nine months and, although I believe from recent letters of inquiry that they are approximately cured for they are both back to slightly restricted former work, I have placed them in the markedly improved group until further examination In Case 12 a subacute type of tuberculosis with fibrous adhesions and considerable myocardial damage was present The patient has been moderately active but is unable to follow any regular occupation one year and one month after operation His condition is not more than moderately improved and I believe it is questionable whether it will greatly improve in the future In Cases 13 and 14 sufficient time has not elapsed since the operation to determine the end-result At present, three and five months after operation, these patients are showing progressive improvement and I believe from their present progress that the ultimate result will approximate a cure

In Case 15, the disease was of long standing and there was a marked degree of myocardial and hepatic damage. This is the only patient in my series who has had two operative procedures. It is now six years and six months from the first operation and five years following the second operation, and his condition cannot be considered more than improved. While he is now able to carry on moderate activities, he continues to have a moderate degree of ascites. After this length of time, I do not believe his condition will ever improve to approximate a cure.

The remaining three patients (Cases 16, 17 and 18) made satisfactory recoveries from the operation but have died subsequently, two from continuation of the disease and one from other causes. In Case 16, the etiologic agent was tuberculosis. The patient made a moderate improvement following the operation for a period of two years and then his condition gradually declined and he died of tuberculous peritonitis two years and three months following the operation. In Case 17 improvement occurred for seven months after operation at which time an influenzal type of pneumonia developed and caused death. This boy, age 15, although he had a long-standing disease and considerable myocardial damage, would ultimately have had a satisfactory result from the operation, I believe, if pneumonia had not developed. In Case 18 the patient's condition was not satisfactory before operation because of marked hepatic damage, Grade 3, and it was impossible to reduce the amount of fluid in his abdomen or pleural cavity. At the time of operation there was a marked degree of myocardial degeneration and considerable encapsulated fluid. His condition improved only slightly after operation. He became gradually worse and died two years and one month following operation from progressive cardiac failure.

Six patients (Cases 19, 20, 21, 22, 23 and 24, Table IV) died in the hospital after operation. One patient (Case 19) died on the twenty-ninth day after operation of left pulmonary tuberculous empyema and multiple pulmonary infarcts. This patient had subacute tuberculous pericarditis, with effusion. His convalescence was satisfactory until the seventh day when the respiratory rate increased and fever and signs of pleural effusion developed. His condition gradually became worse. He became irrational and died on the twenty-ninth day from multiple pulmonary infarctions and tuberculous empyema. Another patient (Case 20) had extensive tuberculous pericarditis, myocardial damage and pulmonary tuberculosis. The essential cause of his death 13 days after operation was cardiac failure and left tuberculous empyema with congestive bronchopneumonia. In Case 21, the patient died on the fourth day after operation from cardiac failure as a result of myocardial degeneration. This patient had had a Talma-Morison operation. In Case 22, the patient died on the third day after operation from cardiac failure and bilateral bronchopneumonia. Examination of the heart, in this case, revealed a large plaque of calcium which extended throughout the entire wall of the ventricle and presented into the ventricular chamber of the heart. In Case 23, the patient was a frail girl, age 15, who weighed 75 pounds (34 Kg) when

she was first admitted to the Mayo Clinic in September, 1943. At that time she was extremely ill and her temperature was elevated daily. It seemed questionable whether surgical treatment would be advisable. However, her condition began to improve in about two months and after a period of four months she was free of fever and had gained five pounds (2.3 Kg) so that operation seemed justified. The operation was without incident, but she died on the third postoperative day of multiple pulmonary embolism. This patient had had digitalis prior to her operation.

In Case 24, death occurred suddenly at the time of operation from cardiac failure. This is the only immediate surgical death in this series. There were no technical complications during the operation. The heart failure occurred after the pericardium had been completely separated but before it had been resected. The heart suddenly stopped during the period of rest when hot sponges were being applied over the pericardium and heart muscle. The patient was frail and had lost considerable weight but after being under preoperative treatment for a month and a half his condition improved moderately and it was felt that surgical treatment was justified. At necropsy the only finding was that of a marked degree of atrophy of the myocardium.

#### REPORT OF CASE I

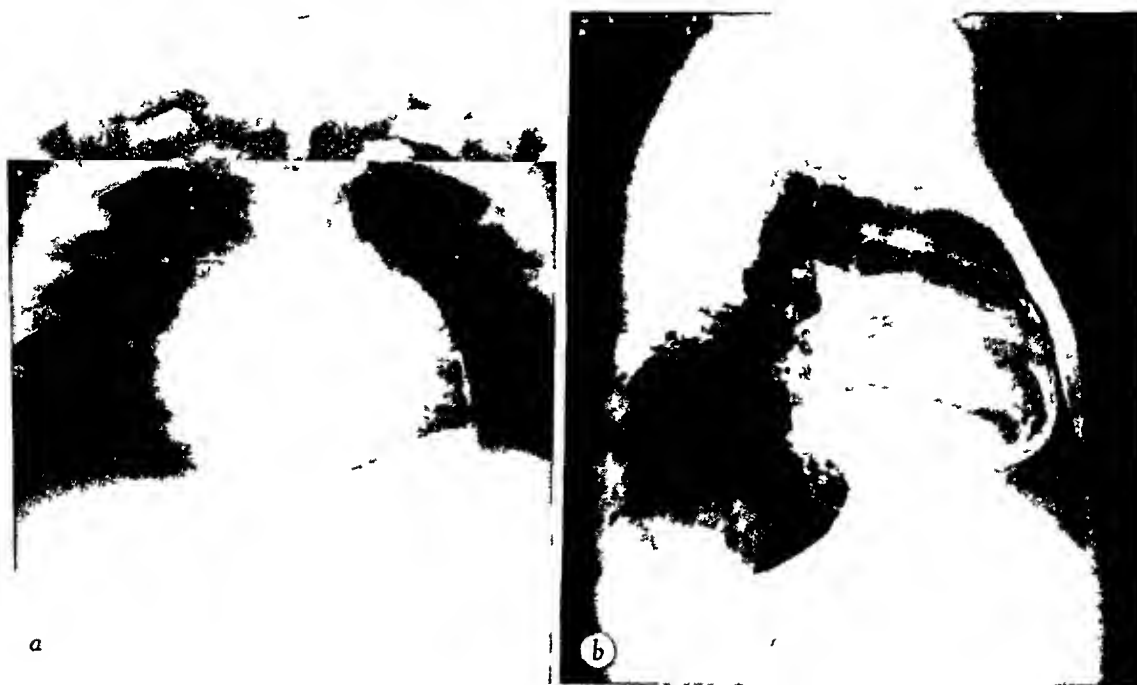
The patient, a man, age 27, was admitted to the Mayo Clinic on April 11, 1938. No definite etiologic factor could be found for his condition. He had had three attacks of pneumonia 15, 8 and 6 years prior to his admission. He had not been well since the attack of pneumonia eight years prior to his admission at which time a deposit of calcium was found around the pericardium on roentgenologic examination. His condition became gradually worse until eight months prior to his admission when ascites and edema of the legs developed. Since that time dyspnea, weakness and fatigue had been severe. He also complained of considerable gastric distress and anorexia.

At the time of his admission abdominal paracentesis was required every six to eight days. The liver was greatly enlarged and a test of liver function revealed retention of dye, Grade 3. The veins of his neck were distended. The venous pressure was 310 Mm of water. The circulation time, determined by means of the intravenous injection of sodium dehydrocholate, from the arm to the tongue was 43 seconds. Systolic blood pressure was 108 Mm of mercury and the diastolic was 80 Mm of mercury. The electrocardiogram revealed a cardiac rate of 90 beats per minute, auricular fibrillation, notched QRS in lead I, slurred QRS in leads II and III, and questionably inverted T waves in standard lead IV. The roentgenograms taken on admission revealed enlargement of the heart shadow with extensive calcification of the pericardium (Fig 3 a and b). On roentgenoscopic examination reduction in the amplitude of cardiac contractions was noticed. Preoperative treatment for elimination of fluids from body tissues was instituted.

*Operation*—May 9, 1938. Marked thickening of the pericardium and epicardium was found together, with extensive deposits of calcium on and between these layers. The scar was adherent over the entire myocardium. Extensive epicardiolysis was performed over both ventricles and the right auricle to the vena cava orifice, with resection of a large portion of the pericardial and epicardial scar from the anterior and lateral surfaces of the heart (Fig 4a). Cultures of the pericardial scar were negative and microscopic examination of it revealed inflammatory tissue and calcium, without any evidence of tuberculosis.

# CHRONIC CONSTRICTIVE PERICARDITIS

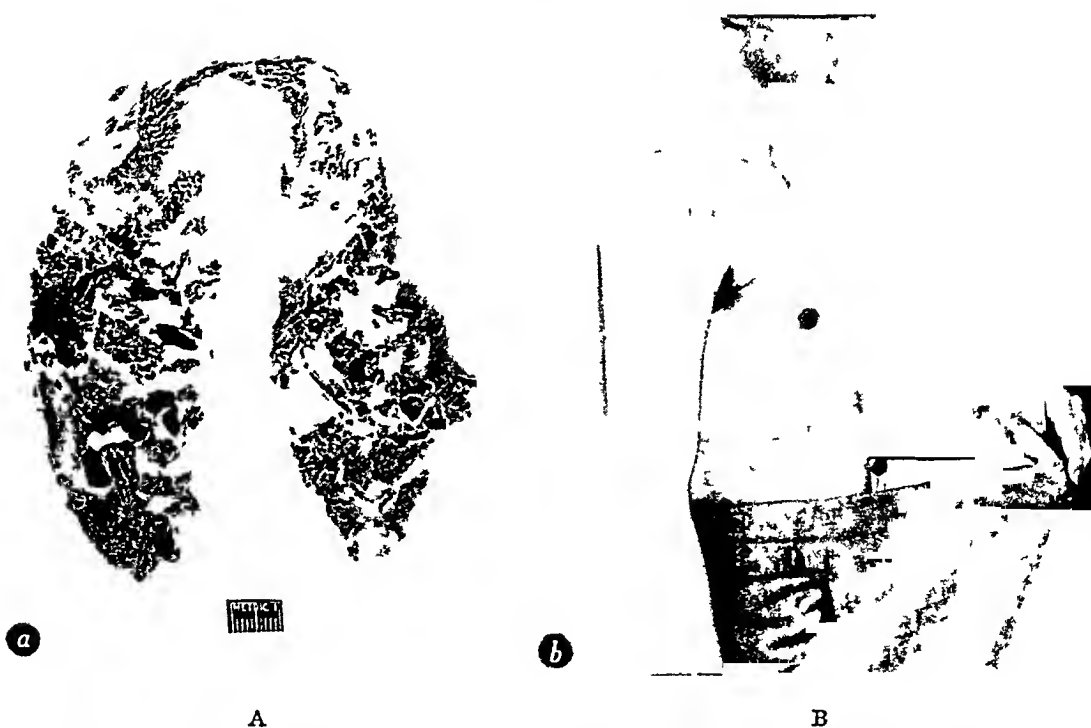
The immediate convalescence was satisfactory. Influenza developed two weeks after the operation which delayed the convalescence somewhat. At the time of dismissal two and one-half months after operation, the ascites had almost disappeared (Fig 4b). Tests of liver function revealed retention of dye Grade 2, whereas before operation it was Grade 3. The venous pressure was 156 Mm of water, whereas, before operation



A

B

FIG 3—Enlargement of the heart shadow and deposits of calcium at time of admission, *a*, anteroposterior and *b*, lateral views



A

B

FIG 4a—Typical pericardial scar and calcium removed at operation together with the cartilages resected from the wall of the thorax. *b* (Case 1). Marked reduction in the size of the abdomen after operation owing to relief of ascites is indicated by size of waistband of trousers worn by patient on admission



it was 310 Mm The circulation time was 20 seconds, whereas, before operation it was 43 seconds The patient gradually improved for nearly two years At the end of that time he was considered cured He is now leading an active and useful life

## COMMENT

The results obtained for the 18 patients who recovered from operation, I believe, are satisfactory Nine of these patients are considered cured The term "cured" is used in a restricted sense to designate the results of these operations It means here the relief of subjective symptoms and the rehabilitation of the patient to his former or some useful occupation The actual damage to the heart undoubtedly is not entirely relieved and the life expectancy of these patients is probably not as great as it could have been had they not been afflicted by the disease The condition of two more patients has improved markedly and their improvement has approximated a cure Operations have been done only recently in two other cases in which progressive improvement has occurred These four patients may ultimately be considered cured, thus making a total of 13 of this series of 24 patients who ultimately may be considered as cured

Of the remaining five patients who recovered from the operation two have shown a moderate degree of improvement but it is not likely that they will ever be considered as cured Three patients have died since the operation The deaths of two of these three patients were due to continuation of the disease One was due to progressive cardiac failure and the other to tuberculous peritonitis In the remaining case the patient was improving satisfactorily from operation but unfortunately died of pneumonia seven months after operation

A review of the six cases in which death in the hospital followed the operation, indicates that a satisfactory result probably would not have been obtained in three Two of these patients had extensive tuberculosis and the other extensive myocardial degeneration with calcification of the wall of the ventricle The remaining three patients who died in the hospital were children and all were in poor general condition because of the long duration of the disease On examination of the hearts at necropsy, marked atrophy of the muscle was found Inasmuch, as regeneration of the myocardium is more likely to occur among younger patients, it is unfortunate that the lesion was not recognized and operation instituted early in the course of the disease in these children

The mortality rate in this series of cases is 25 per cent Although this is relatively high, it is commensurate with the seriousness of the disease, and the mortality rate would have been 100 per cent without surgical intervention It is to be remembered that 11 of these 24 patients (46 per cent) can be considered cured at this time and two additional patients may subsequently improve to this degree of recovery I believe that the percentage of cures can be increased greatly by earlier recognition of the disease and the institution of surgical treatment

Those patients who respond to operative treatment present one of the most dramatic results obtained from surgical procedures, and it is most gratifying to see that these patients who are doomed to a slow, lingering death may be restored to health and usefulness

#### REFERENCE

- <sup>1</sup> Harrington, S W, and Barnes, A R Diagnosis and Surgical Treatment of Chronic Constrictive Pericarditis South Surgeon, 9, 459-484, July, 1940

DISCUSSION—DR JOHN ALEXANDER, Ann Arbor, Mich A matter worth mentioning is the probable value of a two-stage operation for those patients who have had evidence of cardiac constriction for a year or more, and who presumably have an atrophied myocardium

I recall that about ten years ago I extensively released both the left and right ventricles at one operation in a patient who had had cardiac constriction for a number of years The heart dilated and the patient died seven days after operation Since then Doctor Haight and I have operated in two stages in those few patients whose myocardial sufficiency was probably considerably impaired, freeing that part of the heart to the left of the midline at a first operation, and to the right of the midline at a second operation, if the signs and symptoms were not adequately relieved one or more months after the first operation Most of the patients have not needed the second or right-sided stage, we have employed two stages in three patients, without a hospital death

Incidentally, we have been surprised by the absence of severe reactions from pericardiectomy in our cases of chronic tuberculous pericarditis

DR CLAUDE S BRCK, Cleveland, Ohio I do not think we should have any difficulty in the recognition of this condition As a matter of fact, I think quite frequently you can make a diagnosis by inspection of the patient alone You cannot always do that, but you can do it in some patients

There is a very simple diagnostic triad for this condition which I should like to present to you, if I may

The term which I like to apply to this condition is "compression scars of the heart" instead of "constrictive pericarditis" Here is the diagnostic triad which I think makes the diagnosis perfectly simple and infallible

The most important features of the triad is a small, quiet heart A compressed heart is a small atrophic organ The muscle fibers are smaller than normal We showed that some years ago This type of heart is atrophic, it has undergone atrophy of disuse

I should like to point out that the heart in this condition does not waste any energy It is a perfectly efficient "pump" There is no valve leakage The only thing is it does not get enough work to do It does not receive enough blood to do the normal quota of work, and it undergoes atrophy from disuse, and that is why when you take the scar off you get an immediate improvement, and then later on you get a delayed improvement because this atrophy from disuse requires time for it to disappear A compressed heart cannot dilate nor can it hypertrophy

The fluoroscope usually helps you to recognize a quiet heart, but the shadow you see in the roentgenogram or in the fluoroscope is not always just heart—it is heart plus the compression agent, and the compression agent may be in some cases fluid, blood or pus It may be a tumor, and in other cases it may be quite a thick scar

As Doctor Harrington has shown, the scar may be one centimeter or more in thickness The shadow may appear to be large, whereas, the heart actually is a small organ

The other two components of this triad refer to the superior and inferior vena cava These structures always contain blood under pressure When the venous pressure rises to a level of 18 or 20 cm then the fluid part of the blood begins to filter through the capillary bed, and you get ascites It is ascites that takes the patient to the doctor

Usually the patient does not know he is sick until he gets ascites. We can use this information for diagnosis. A patient with ascites does not have a compressed heart unless the venous pressure is 18 or 20 cm, or higher. The ascites refers to the inferior cava, and the high venous pressure in the arm refers to the superior vena cava.

The triad consists of a small shrunken heart, plus ascites, plus venous pressure in the arm which is 18 or 20 cm of water, or a pressure higher than this level. This triad cannot be wrong.

There should be no difficulty in differentiating this condition from cirrhosis of the liver, because you do not have a quiet heart with cirrhosis of the liver and you do not have an increase of the venous pressure in the arm.

I performed 51 operations for removal of compression scars on 46 patients. The results are shown in Table I.

TABLE I

Operative mortality	1—2 2%
Postoperative deaths	
From tuberculosis	4—8 7%
Other causes	4—8 7%
Subsequent mortality	4—8 7%
Living	
Cured	31—67 47%
Improved	1—2 4 3%
Total cured or improved	33—71 7%

I should like to comment upon these results. The operative death occurred in the eighth case of the series in 1934. Death was due to ventricular fibrillation. It occurred suddenly and without warning. I believe I can state the cause of fibrillation. It was set-off, as by a trigger, while the scar was being dissected by scalpel from the descending ramus of the left coronary artery. The scar was being rolled back on my index finger for the dissection and this, in turn, I believe, occluded this coronary artery. An area of anoxemia developed in the myocardium and this became a trigger which, like a trigger in the brain, set-off a convulsion. I was not able to defibrillate the human ventricles at that time. An effective method for this did not exist. At the present time this complication could be taken care of without any difficulty. We have an effective method for defibrillation of the ventricles.

There were eight postoperative deaths. Four were due to tuberculosis, two were due to infection, and two were due to acute dilatation of the heart. The patients with tuberculosis had extensive and severe involvement of pleura, pericardium and mediastinal structures. These deaths can scarcely be attributed to operation. The cases were inoperable, and the patients were close to the point of death before operation. The infection in the other two cases may have been lighted-up by the operation. There is no way of determining this. The patients were afebrile before operation. In the remaining two patients it might have been possible to have prevented acute dilation of the heart by blood-letting. There are two factors related to this subject. One is the atrophic heart, without the compression scar around it, has a tendency to dilate. The other factor concerned with dilatation is the fact that the blood volume is increased in this condition. Unpublished data, from a study of this series of patients, indicate an increase of about 30 per cent in the circulating blood volume. So that there is an increased blood volume to be moved by the heart. The four patients who died after discharge from the hospital were improved, insofar as compression of the heart was concerned. One developed miliary tuberculosis, and died several months after operation. One developed pneumonia, and died several years later. One developed recurrence of compression, and died several years later. One died of unknown cause.

There are 33 patients who are now living. In some of these patients the operation was performed 15 years ago, and the patients are cured. Thirty-one of the entire group are cured. They are completely free of ascites. Two patients are classified as improved.

They may be completely cured. One of these had a tuberculous scar, and I have not seen her recently but it is reported that the abdomen is not enlarged. The other patient had reoperation recently because of recurrence of compression scar. He may be cured.

I should like to add that no bad-risk patient was refused operation. The only requirement for operation was the diagnosis of compression scar. We have never made a mistake in the diagnosis. If the patient was febrile, a period of bed rest was given before operation. If the fever failed to subside and if the condition became worse, operation was done regardless of risk. Several lives were saved by this program.

I feel that these results are a good score. The compression scar must be removed wherever it exists. Ventricles, auricles, venae cavae must be relieved of any compression in order to obtain a cure. Partial operations yield partial results and increase the probability of recurrence of scar.

DR GEORGE J. HEUER and DR WILLIAM DEW. ANDRUS, New York. Discussion by the authors presented by Doctor Firor, in the absence of both discussers.

"Eighteen patients have been subjected to 19 operations, without an operative or a postoperative fatality. Of these, (1) seven patients are classified by us as cured over periods varying from one and a half to eight and a half years, of whom six have been followed more than three years, and three more than seven years. Of these seven patients, one after being completely cured for three and a half years, died from an unrelated acute generalized peritonitis.

"(2) Three patients more recently operated upon have shown such improvement in their symptoms and signs as to warrant the expectation of a cure. Since they have been followed less than one year, they have not, however, been classified as cured.

"(3) Four patients are markedly improved over periods of from three to six and a half years. One of these patients died six and a half years after operation from pneumonia.

"(4) One patient is markedly improved, and is living six years after operation.

"(5) Four patients were not improved by the operation. Of these, one is living seven years after operation, and three have died. One patient died one year after operation from recurrent pulmonary infarction, and two died 11 months and seven months, respectively, after operation from a progression of the disease. In the last two, it became evident on their return visits that the operation had failed in its purpose.

"A summary of these results shows that 14 out of 18 patients subjected to operation have been cured or markedly improved."

# THE PROBLEM OF EMBOLISM OF THE PULMONARY ARTERY\*

## REPORT OF A TRANSCARDIAC OPERATION

HAROLD NEUHOF, M D

NEW YORK, N Y

IN ALL PROBABILITY the massive and usually fatal form of pulmonary embolism will be rarely encountered when the prophylactic measures now in the process of development are fully evolved and generally applied. At the present time, however, massive pulmonary embolization is not rare and a consideration of its surgical management may, therefore, not be amiss.

The Trendelenburg operation for embolism of the pulmonary artery is the sole measure which has been employed in the past three decades. Because of its formidable nature the operation is believed to be indicated only in those cases in which a sufficient period of observation has elapsed to be assured that death is impending. According to the surgical literature, it would appear that the diagnosis as well as the situation and the physical features of the embolus have been more or less taken for granted. Various features of the embolus have been described but not in relationship to the question of operative removal. I believed that a detailed examination of well-documented cases might provide information of surgical significance which was lacking in the literature. A study was made by S. Kleinf† and myself of 88 consecutive autopsied cases encountered at the Mount Sinai Hospital. The work will be described fully elsewhere but certain pertinent features can be briefly set forth at this time.

Owing to some question as to the cause of death in cases of massive pulmonary embolization it should be said that the study appears to show that obstruction of the pulmonary artery is the essential cause. The factors producing death were obstruction, asphyxia, and heart failure. The fatal episode took place at virtually any time during a medical illness (26 cases) or in the surgical postoperative period (62 cases). Of the 62 deaths in operative cases 21 occurred in the first week, and of these, 14 in the first few days. Only 26 were encountered in the second week, chiefly in the classical period of the eighth to the twelfth day. Some details will be given later concerning the time of death in relationship to the onset of symptoms.

An analysis of the 88 cases reveals that there was evidence at autopsy of previous *peripheral* embolization in 43, that is, in half the cases. Thirty-six of the patients had had symptoms and signs related to such earlier episodes, and in at least 13, there were local manifestations suggesting the presence of thrombosis or phlebitis. If argument were needed, these data would supply

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\* Read before the American Surgical Association, May 3-4, 1944, Chicago, Ill.

† Now Major, M C, A U S

a powerful one for thorough-going prophylactic measures in any hospital service, medical or surgical

The variations in the size, shape, and position of the pulmonary embolus were studied and were found to be of surgical significance. Some emboli were extremely long, with twig-like branches, others short and curled up. Some were firm, others friable. A few were firmly adherent. The embolus was situated (1) in the outflow tract of the pulmonary artery, (2) in the main trunk, (3) in one or more of the major branches, or (4) fragmented and distributed in the lesser branches. Thus, it is obvious that the chances of encountering and removing the embolus at operation cannot be gauged in advance.

The symptoms in the 88 cases were those of asphyxia, shock, syncope, or heart failure, singly or in various combinations. Variations in symptoms and signs often made an absolute diagnosis difficult or impossible except in classical cases. Central and peripheral blockade could not be differentiated. Perhaps the most significant conclusion from the study of symptoms was that there was no dependable relationship between the degree, location, and extent of the pulmonary embolus, and the clinical picture. The literature scarcely deals with this aspect of the subject and yet the question must be raised as to when, if ever, as formidable a procedure as the Trendelenburg operation is indicated.

Although the classical cases can be recognized readily, it can be said that the differential diagnosis from coronary thrombosis, in particular, or non-cardiac lesions, in general, may be difficult or virtually impossible. The electrocardiogram was not of decisive aid in the differentiation from coronary thrombosis. In our 88 cases an unequivocal diagnosis of pulmonary embolism was made in 16, an equivocal one in 13. The diagnosis was incorrect in 22. The clinical picture in 13 cases did not appear to suggest or, at any rate, did not warrant a diagnosis of pulmonary embolus.

From a consideration of the topographic features alone, embolectomy would have been feasible in 33 of the 88 cases. However, amongst these 33 cases there were no distinctive clinical features to differentiate them from less favorable cases. The conclusion is, therefore, inevitable that an operation always must be regarded as an exploratory one. Of the 88 cases, almost half were suffering from otherwise irremediable conditions. A survey of all the features of the 88 cases including diagnosis, duration of symptoms, topography of the embolus, *etc*, establishes that there were between 15 and 26 cases spread over a period of ten years in which favorable criteria for embolectomy existed.

The occurrence of death after the onset of symptoms was within ten minutes in 18 cases, in 11 to 15 minutes in nine cases, in 16 to 30 minutes in 11 cases, and in one-half to one hour in eight cases. Twelve died in one to four hours, six in four to ten hours, five in ten to 24 hours. Thus, a significant fact concerning the cases to be regarded as favorable for embolectomy was that the duration of life was short in many. This is quite out of line

with the protracted duration for which the Trendelenburg operation has been advocated. In this connection, reference should be made to a number of cases studied but not included in this series, characterized by extremely severe clinical manifestations of prolonged duration with recovery ensuing after death was anticipated. Some of these cases conform to the type in which the Trendelenburg operation might have been performed in accordance with the formula of observation over a period of hours.

The study of the 88 cases has shown that an operation for the removal of pulmonary embolus can be only rarely indicated. In 1938, there were collected 132 cases in which the Trendelenburg operation had been performed, with a mortality rate of 93.2 per cent. Seven patients recovered. There have been at least two successful cases since that time. It is clear that some lives have been saved which otherwise would have been lost. However, the unfavorable features are (1) an extremely high mortality, (2) the requirement of a very hasty operation because of the short period of permissible occlusion of the pulmonary artery, (3) a too formidable operation in case of error in diagnosis, (4) an unsuccessful operation if the embolus is not of classical topography and in the typical situation, (5) the requirement of a specially trained team, and (6) the limitation of operation to a rare clinical variety of pulmonary embolism.

It is believed that some of the objections to the Trendelenburg operation are met in the operation which was performed in the following case.

**Case Report**—Mount Sinai Hospital No 498441. E. P., male, age 18, an athlete, had been well until 16 days before admission. There then began a left lower lobe pneumonia, with treatment by sulfathiazole and subsidence in a few days. Four days before admission there was an episode of pain in the right lower chest and shoulder, and fever, with subsidence. The evening prior to admission there was an attack of left chest pain. Three hours before admission there was a sudden access of left anterior thoracic pain, a chill and severe dyspnea. His physician found signs of vasomotor collapse with a rapid thready pulse, cold and cyanosed extremities, and an unobtainable blood pressure.

This was the condition on admission at 10 A.M. By 11:30 A.M. there was some improvement, apparently the result of the administration of oxygen and morphine. A systolic blood pressure of 85 was obtainable by auscultation. An electrocardiogram revealed changes which were compatible with acute cor pulmonale or pulmonary embolus. The chest film disclosed no definite abnormality in the lungs. Papaverine was administered intravenously and heparin shortly thereafter. The improvement which began shortly after admission was transient. By 4 P.M. the pulse was imperceptible at times, the systolic pressure 70, the patient semicomatose. At 4:50 P.M. the patient was comatose and the general condition poor. There was slight improvement thereafter, apparently the result of a transfusion of blood. There were periods of partial consciousness but the pulse and blood pressure became scarcely obtainable, the heart sounds faint, and the vasomotor collapse extreme. At the time of operation, 8:45 P.M., the patient was not responsive and death appeared imminent.

**Operation**—Local anesthesia was employed but there appeared to be little need for any form of anesthesia. A right parasternal incision was made through the fourth and fifth costal cartilages and the adjacent portion of the sternum was removed with rongeurs. A substantial proportion of the pericardium was exposed extrapleurally and

was incised. The right auricle and ventricle which were pulsating with little force were well visualized. By palpation the pulmonary artery appeared empty of thrombus, but of this one could not be sure. Two parallel silk sutures were placed through the most prominent portion of the right ventricle and an incision through the wall of the ventricle was made between them. The escape of blood was stopped effectively by the introduction of an open-end No. 34 F catheter (child-sized rectal tube) and the crossing of the sutures over the catheter. The catheter was passed upwards the short distance necessary to bring it to the outflow tract of the pulmonary artery and suction was applied. The blood was drawn and filtered into a flask containing citrate solution with the intention of returning it into the circulation. When thrombotic material was not observed in the gauze filter the catheter was withdrawn from the ventricle and saline solution drawn through the system in order to see if a thrombus had been extracted. The crossing of the two sutures after the withdrawal of the catheter prevented escape of blood from the ventricle. The catheter was then introduced and removed a second time and, again, no thrombotic material was withdrawn. The maneuver was again repeated, the catheter being passed into the pulmonary artery this time. No thrombotic material was obtained, the catheter was withdrawn, the sutures were tied across the incision in the ventricle, and one additional suture was introduced and tied in order to stop some leakage of blood. The duration of operation to this point was one-half hour. Death occurred 15 minutes later.

*Autopsy*—This disclosed an empty main trunk of the pulmonary artery. Thrombi filled the right and left branches beginning in each instance 2 to 3 cm from the main trunk. They extended into the smaller branches on both sides. They were friable and, microscopically, revealed beginning organization. The lungs showed infarcts on both sides. The incision in the heart was found to be about 2 cm in length, situated in the anterior aspect of the right ventricle. When tested with fluid in the ventricle it was found to be well closed.

#### COMMENT

The foregoing operative procedure is simple, reasonably safe, and does not require undue haste. Special skill and practice and a special team are not needed. The suction of blood, which results in some measure of decompression of a right ventricle laboring unavailingly against the obstructing embolus, is a desirable feature. However, the essential part of the operation is performed blindly and does not provide assurance that suction will, in fact, engage the thrombus in the eye of the catheter. A metal tube with an appropriately hollowed end would probably be more effective in engaging and extracting the thrombus. Despite the fatal issue in the reported case, further attempts to extract a pulmonary embolus through the right ventricle appear justified.

*DISCUSSION*—DR CLAUDE S. BECK, Cleveland, Ohio. This procedure described by Doctor Neuhof, I believe, has much to commend it. I used this same method years ago in the experimental laboratory. In these experiments a glass suction tube was introduced into the right ventricle and directed into the conus arteriosus and pulmonary artery and emboli consisting of pieces of skeletal muscle were removed from the pulmonary artery. The control sutures and the method of controlling hemorrhage were precisely the same as those described by Doctor Neuhof. (Ref. Beck and Cutler, *Journal Experimental Medicine*, 40, 375, 1924.) I did not apply this method to human patients, and I refer to these experiments simply to indicate familiarity with this method.

Anyone who has performed the Trendelenburg operation will agree with Doctor Neuhof that it is a formidable one. Surgeons do not have much taste for this operation.



It is difficult to get adequate exposure. It is difficult to place the rubber tube under the pulmonary artery so that it can be elevated and controlled. Orientation is difficult, and the aorta has been opened instead of the pulmonary artery. In view of these considerations, the surgeon elects to undertake the Trendelenburg operation only after the patient has expired—when the risk of operation no longer exists. It then becomes a race with time. The oxygen system must be restored before irreversible damage to the breathing center takes place. *The chances of success under these circumstances are, indeed, slight.*

This other method has several considerations in its favor. Exposure of the right ventricle is not as formidable an operation as is exposure of the pulmonary artery. Orientation is not difficult. The right ventricle is readily recognized. Control sutures are easily placed. There is no special difficulty in making an incision in the right ventricle and controlling the wound so that it does not bleed. The conus arteriosus is accessible and it leads directly into the pulmonary artery. A suction tube can be readily introduced. The incision in the ventricle can be readily closed by suture.

There is another consideration in favor of this method. It seems to me that this operation can be performed with relative safety. Experience with the method will be necessary to determine this point. If the operation can be undertaken with reasonable safety then it can be applied before the heart stops beating. This would be an important consideration because it would remove the race with time, and every care could be taken to make it safe. It should be emphasized that the heart beat is not disturbed in performing this operation. The extraction of the clots need not interrupt the circulation. The suction tube can be inserted as frequently as necessary to remove all clots. A glass or metal tube is better than a catheter. It is unfortunate that embolic material was not successfully removed in this first human patient. The clots extended into the smaller branches on both sides. These clots, no doubt, were extensions from the original embolus. Early removal of the primary embolus might have prevented formation of these secondary clots. The best time to clear the vascular tree is early after the embolus strikes, and if the operation becomes a relatively safe procedure surgeons will be more inclined to apply it early—before the patient dies.

DR ALTON OCHSNER, New Orleans, La. I cannot refrain from speaking about this operation which Doctor Neuhoﬀ has described, and which of course is an ingenious one. I think that we, as members of the surgical profession, should try to prevent these complications and not perform an operation that has to be undertaken immediately before death. There is no reason why anyone should ever develop a pulmonary embolism now, I believe.

There are two types of intravascular clotting, one which is associated with inflammation of the vein wall, *i.e.*, thrombophlebitis and another in which there is a bland thrombus with no associated inflammation of the vein. The latter we have designated as phlebothrombosis.

The former seldom gives rise to embolism because the clot is firmly attached. Fortunately, the condition is easily diagnosed. Embolism rarely occurs in cases of suppurative thrombophlebitis, which is usually associated with a pelvic infection. In contradistinction to thrombophlebitis, in which the diagnosis is easily made, the diagnosis in phlebothrombosis is not obvious and can only be made by being on the look-out for it. These patients get along fairly well postoperatively and have few symptoms. By *looking for vein tenderness* the condition can be suspected and the diagnosis can be made by phlebography. These are the cases in which pulmonary embolism is likely to occur because the intravenous clot is a red thrombus and is not firmly attached to the vein wall, and can be detached easily. Ligation of the involved vein above the site of the thrombus will prevent detachment of the clot and pulmonary embolism, obviating the necessity of waiting until the patient becomes moribund, with a massive embolism, in order to perform the acrobatic surgery in order to remove the occluding thrombus in a dying individual.

More important than the prevention of the detachment of an intravenous clot is the prevention of the original thrombosis. This can usually be accomplished by increasing the circulation through the lower extremities. Every patient past 40 years of age, who is put to bed at all, should have his extremities wrapped from his toes to his groin with ACE bandages. In that way the circulation in the deep veins is speeded-up by compressing the superficial veins.

Immediately postoperatively, when he comes back from the operating room, he should be placed in the Trendelenburg position, unless there is some contraindication, until he is able to move forcefully his extremities.

If one will do this and prevent the increased intra-abdominal tension, and also prevent the decreased respiratory excursion, intravenous clotting usually can be prevented. These patients, particularly the older ones, should be watched for vein tenderness.

We are all familiar with the work done by the Swedes a number of years ago in the Trendelenburg operation, and the story of how they sat at the patient's bedside after he got his first pulmonary embolism, and waited until he was just about dead, and operated then. They saved a few, it is true, but there is no reason why we should allow this to occur.

I hope we will not have any more papers on the removal of pulmonary emboli before this organization, an operation which should be of historical interest only. Certainly, the way to prevent death from pulmonary embolism is to prevent the clot from being detached and getting into the pulmonary vein if thrombosis does occur. If this is done, pulmonary embolectomy is unnecessary.

DR CLAUDE S. BECK: I take issue with the wishful thinking of Doctor Ochsner concerning pulmonary embolectomy. This complication will occur in the future and the development of any safe method for removal of pulmonary emboli will be a welcome contribution. I am certain that we all go along with him in his attempts to prevent pulmonary emboli but I cannot simply assume that this complication will be wiped out and will not occur, and we need not concern ourselves with removal of pulmonary emboli. The methods for prevention of pulmonary emboli have not become established or generally accepted. An embolus may arise in the vein proximal to the site of ligation and a fair percentage of emboli arise from sources other than the veins of the legs. They may arise from the abdomen and abdominal viscera. Until it can be shown that this complication can be prevented, we shall be interested in treating pulmonary emboli.

# EFFECT OF SULFONAMIDES UPON EXPERIMENTAL GUNSHOT WOUNDS INVOLVING PERIPHERAL NERVES\*

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INJURIES OF THE PERIPHERAL NERVES which result from war wounds are usually associated with extensive soft tissue destruction and fractures of the bones. In any event, they are contaminated or grossly infected so that the liberal use of the sulfonamide drugs at the time of injury or débridement is to be considered in an effort to control the course of the infection. It is of importance, therefore, to know what effect the sulfonamides might have upon the repair and regeneration of the peripheral nerve. If the use of the sulfonamide drugs will allow a peripheral nerve wound to be repaired after a shorter interval following injury without the danger of the development of a suppurating wound, and if they have no deleterious effect upon nerve regeneration, then the ultimate functional results of the repair of nerve injuries will be improved.

The aim in this study was to produce a wound with tissue destruction and severance of the sciatic nerve, the severity of which could be compared to the usual wounds of modern warfare. The wounds were produced at short range by .22 caliber, long rifle, lead-tipped bullets whose tips were countersunk, or coned out, and which had a muzzle velocity of approximately 1070 feet per second. The wounds were uniformly characterized by a small round entrance on the lateral aspect of the thigh and a much larger, irregular and ragged area of exit on the medial aspect. The left leg of the anesthetized cat was suspended with full extension of the knee and the thigh slightly compressed in its mediolateral axis by two wooden surfaces, thus, immobilizing the soft tissues and reproducing the effect of an active muscle holding the nerve taut. An adequate opening in the lateral compressing board presented an unobstructed path for the bullet. This method resulted in a fairly constant and uniform severance of the left sciatic nerve and less frequently a fracture of the femur. Without compression of the thigh the nerve was usually only contused and pushed aside by the bullet. Prior to the injury, the animal's thigh was shaved in order to prevent a too virulent and too massive wound infection. After the bullet wound was inflicted, a simple clean gauze dressing was applied and allowed to remain in place until the wound was débrided.

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Débridement of the wound and simultaneous repair of the nerve were performed immediately, and at various intervals, until 48 hours after the injury. Of the 217 gunshot wounds studied, 74 were débrided immediately after injury, 27 after 6 hours, 15 after 12 hours, 26 after 18 hours, 53 after 24 hours, and 22 between 24 and 48 hours. Nerve repair and closure of the wound were performed in every animal despite the length of time which had elapsed between the injury and débridement. All surgical procedures were undertaken with strict aseptic precautions. Wound repair was preceded by cleansing the skin thoroughly with soap and water, followed by iodine, alcohol, and draping. The exit wound on the medial aspect of the thigh was first repaired. The débridement was complete, insofar as all questionably devitalized tissue was completely excised. The skin edges were trimmed, the edematous subcutaneous tissue and the traumatized dusky red, or purple, discolored muscle was removed. All foreign bodies were removed. The wound was irrigated with saline solution and closed in layers with interrupted silk sutures and skin clips. The same procedure was used in closing the wounds of entrance, except that the exposure of the injured nerve required an incision sufficiently long to reflect the lateral musculature of the thigh.

Repair of the nerve was carried out after complete débridement and irrigation of the wound had been accomplished. The bullet produced an irregular and ragged severance of the nerve, and the nerve fascicles protruded from the epineurium and perineurium of the torn ends. The epineurium had usually retracted for a distance of three to eight millimeters. Small blood clots were found around the epineurium and perineurium, and the epineurium appeared swollen, glossy, and seemed to contain clear fluid. Ecchymosis, discoloration, and edema affected both torn segments for a distance of 10 to 15 millimeters, and the nerve showed a parallel striation which was perpendicular to its course, and resembled muscle striae. Although the course of the bullet had been straight when piercing the thigh, the shot canal was found not to be continuous because the muscles had changed their position and state of contracture. Thus, the relation of nerve to muscles was changed which explained that frequently the contused or torn nerve was no longer in the area of muscle destruction. Nerve repair consisted of a local neurolysis, trimming of the ragged nerve ends, resection of the severely contused nerve tissue, and end-to-end suture, or implantation of a fresh homogenous graft depending on the amount of nerve destruction. The suture material used was fine black silk.

The gross appearance of the wounds surgically treated after six hours was indistinguishable from that immediately after injury, except for an occasional edema. Wounds which remained untreated more than 12 hours after injury presented characteristic signs of infection. The traumatized tissues became necrotic, grossly edematous and developed an offensive odor. In several cases the entire thigh and leg was tumefied and grossly edematous. The most common organisms found (bacterial cultures taken

just prior to débridement) were *B coli*, *nonhemolytic Streptococcus*, *Staphylococcus albus*, *B proteus*, *B subtilis*, and an occasional diplococcus.

In a series of animals, various sulfonamide drugs were introduced locally into the wound at the time of débridement. The drugs used were powdered and crystalline sulfanilamide, powdered sulfathiazole, and sulfadiazine. They were distributed evenly over the entire wound before closure. One-tenth gram (0.1 Gm) of drug was used per pound of animal weight, giving an average of 0.7 Gm in each wound. The implanted powdered drugs developed a paste-like consistency, especially around the nerve, and were absorbed so slowly that three to seven days were required before they had disappeared from the wound surfaces. Sulfanilamide was used in 37, sulfathiazole in 35, and sulfadiazine in 24 animals, while the wounds of 48 animals were not treated with any chemicals.

In 51 instances in which débridement was performed 24 hours or more after injury, a sulfathiazole jelly was introduced into the bullet tract at the time the wound was received. This jelly is water-soluble and contains sulfathiazole in a concentration of 5, 15, or 25 per cent. Three to five cubic centimeters of jelly was introduced into the depths of the wound from a metal tube through a fitted flexible metal conduit. These wounds were débrided in the same way as in the other animals and, in forty, sulfonamides were powdered into the wounds before closure. The sulfathiazole level in the blood was determined at the time of débridement. The average level was 1.69 mg % after 24 hours and 0.33 mg % after 48 hours.

In spite of a careful débridement performed immediately after inflicting the gunshot wound, the rate of infection and formation of extensive abscesses which burrowed along the course of the sciatic nerve and the fascial planes of the muscles was very high when the sulfonamides were not used in the wounds locally. The rate of massive infections increased the longer débridement was delayed. Thus, in the series in which no sulfa drugs were implanted massive infections were encountered in 38.2 per cent of the 34 animals treated immediately after injury, and in 42.9 per cent of the seven animals operated upon six hours after injury. In the 11 animals débrided within 12 to 18 hours after injury, massive infections developed in 54.5 per cent of them, and this incidence grew to 83.3 per cent of the six animals treated after an interval of 24 hours. These infections usually became apparent five to seven days after débridement, repair, and closure of the wounds, and most of them developed rapidly into generalized septicemia and death, even though drainage was instituted as soon as the infection was noticed.

The local application of the sulfonamide drugs in the wounds at the time of débridement did not completely prevent the formation of infection. In this group of animals the rate of infection was also directly proportional to the period of time which had elapsed before the wounds were treated. The incidence of infection was 50 per cent of 40 animals when the wound was treated immediately with powdered sulfonamides or sulfathiazole jelly, 10 per cent of 20 wounds débrided after 6 hours, 26.6 per cent of 30 animals

treated within 12 to 18 hours, and 55.5 per cent of 18 animals treated after 24 hours.

The immediate introduction of sulfathiazole jelly into the wound reduced the incidence of infection, especially in the wounds whose repair was delayed for 24 to 48 hours. When no further sulfonamides were used the rate of infection was 36.3 per cent of 11 animals, and this figure was reduced to 22.5 per cent in 40 cases when powdered sulfonamides were implanted in the wound at the time of débridement.

The toxicity of the drugs as manifested in this series, lies somewhat in the realm of conjecture. Fourteen animals died within two to four days after surgery from uncertain causes. Nine of the deaths occurred prior to the use of the jelly, and five of these animals received no chemicals, while the other four were treated with sulfanilamide and sulfathiazole at the time of débridement. The remaining five animals were in the jelly series, three of which also received sulfanilamide, one sulfathiazole, and one sulfadiazine at the time of débridement. Careful autopsies revealed no clues related to the cause of death. The kidneys of 18 animals were studied histologically and failed to present the changes reported as due to the use of sulfonamides. The considerable amount of large fat droplets in and around the convoluted tubules has been reported in normal cats and there is no reason to believe that the drugs should produce any lipid degeneration. The blood levels obtained after the introduction of the soluble sulfathiazole jelly in the wounds also speaks against the probability of a toxic effect. Furthermore, in the course of experimenting upon such a large number of animals, an occasional debilitated cat was used, and it is only logical that such an animal would succumb from the traumatization or experience a fatal postoperative course.

The extensive débridement of muscle and nerve considerably changed the original nerve bed, the surfaces and the relation of the surrounding tissues. These changes produced an extensive scar formation, and dense adhesions were found around the repaired nerve and usually embedded the suture lines and both central and distal segments for a distance of 10 to 15 millimeters above and below the suture line, which was always moderately swollen. The adhesions were much more severe than those found in other series of animals in which aseptic nerve sections and sutures were performed. Because of the severity of the posttraumatic scar formation only little difference could be noted between the wounds which were treated with the drugs and those which were not. In a few instances, however, thicker and firmer adhesions have been noticed following the use of sulfanilamide powder. The use of the sulfathiazole jelly did not alter the amount of adhesions around the nerve and did not seem to hinder tissue repair in any noticeable way.

From the bacteriologic cultures and the high frequency of serious infections, it is evident that the wounds resulting from gunshot injuries in our experimental animals showed a maximum of gross contamination and of

tissue damage. It was not possible to reduce the seriousness of these infections with immediate thorough cleansing and careful wound excision and perform a satisfactory nerve suture and primary closure at the same time. However, the incidence of infection, when wound cleansing, débridement, nerve repair and closure were performed within 12 hours after injury, was lower in the series of animals in which the sulfonamide drugs were applied locally to the wound.

Another purpose of these experiments was to find out how long débridement followed by immediate nerve repair and wound closure could be delayed without a prohibitive incidence of infection. There was a high incidence of infection when débridement was delayed more than 12 hours, it was very high when the delay was 24 hours or more. The introduction of sulfonamides into the wound reduced the incidence of infection only slightly, and it seemed that immediate nerve repair *after* 12 hours was doomed to failure. During the delay the infection had already progressed to such an extent that débridement and local chemotherapy proved ineffective. Since all gunshot wounds are grossly contaminated, it was only logical to think that local chemotherapy applied earlier could overcome, or at least reduce, the developing infection. It is not possible to introduce the powdered or crystalline drug into the tortuous and complicated wound adequately, and for that reason a sulfathiazole jelly was used which could reach most of the crevices and recesses of the wound. The introduction of this jelly into the wound immediately after the gunshot injury was inflicted reduced the incidence of infection in all of the experiments upon delayed débridement.

If the sulfathiazole jelly prevents bacterial invasion, its effect is only temporary and, therefore, cannot altogether prevent the formation of a later infection in a delayed wound. The early introduction of the jelly is only a preventive measure and there are no reasons to minimize the necessity of surgical asepsis. All such wounds need to be adequately cleansed, débrided, and have additional local sulfonamide therapy before closure to obtain the best results. Thus, the incidence of infection in wounds repaired 24-48 hours after injury was reduced from 83.3 per cent in six animals to 22.5 per cent in 40 animals, when sulfathiazole jelly was introduced into the wound immediately after its receipt, and sulfonamides were powdered into the wound at the time of débridement.

In another group of 156 cats the left sciatic nerve was sectioned surgically, in one group under aseptic conditions and another group without sterile precautions. The nerve was sectioned and repaired immediately by end-to-end sutures in 34 cases, by implantation of an autogenous graft in 57, and by implantation of a homogenous graft in 65 cases. Seventeen of the animals operated upon under septic conditions developed an uncontrollable infection and were disregarded for further histologic or clinical studies. In the remaining 139 animals, powdered sulfanilamide was used around the repaired nerve of 26, sulfathiazole in 28, and sulfadiazine in 23 animals, the remaining 62 animals were not treated with any of the drugs and were

considered as control experiments. One-tenth gram of the powdered sulfonamide drugs\* was sprinkled around the exposed sciatic nerves per pound of the animal's weight, the average dose was 0.7 Gm.

In two animals for each drug, the exposed sciatic nerves were not sectioned, but sulfanilamide, sulfathiazole and sulfadiazine were implanted about the nerve trunks and the wounds were observed at frequent intervals for a period of 48 and 72 hours. The nerve was then removed for study. After two hours the powdered drugs became wet, after five hours the material gathered in large clumps around the nerve, and the presence of clear fluid could be seen in the wounds. This serous exudate increased steadily for 24 hours, some of the sulfanilamide, sulfathiazole, and sulfadiazine powder had been absorbed, however, most of it clung in small clumps to the nerve itself. After 48 hours a large amount of the sulfanilamide had been absorbed, while the sulfathiazole and sulfadiazine clumps were loosely adherent to the nerve and its surrounding tissues. These clumps had the appearance of curdled milk and the consistency of chewed gum. After 72 hours small clumps of sulfanilamide powder were still adherent to the nerve, while the other drugs were still present in large amounts.

The wounds treated with the sulfonamide compounds were characterized by an increased amount of adhesions fixing the nerve to the surrounding tissues. The increase in the amount of adhesions between the epineurium and the surrounding muscles was a constant finding in both end-to-end sutures and in graft repairs, whether or not the operation had been performed with an aseptic or septic technic. These adhesions had a silvery, spider web-like appearance, could be easily torn, and were moderately vascular. They were thicker and more extensive about the grafts, and in some instances fixed the graft to the surrounding tissues so that the nerve had to be dissected away. This distal suture line of the grafts was usually thicker and more often adherent to the surrounding tissues than the central suture, and this condition was more marked in homogenous grafts. However, thicker adhesions and more prominent central and distal suture lines were observed in the grafts treated with the sulfonamides. In general, it appeared that the nerves treated with sulfanilamide powder showed more adhesions than those in which the other two compounds were used, however, this difference was small and could easily be overlooked.

No conclusive evidence was found that the regeneration of nerve fibers, axis cylinder formation, myelinization, or the absorption of myelin decomposition products was changed by the use of the sulfonamide drugs. The deviation and abnormal distribution of regenerating nerve fibers were observed regardless of whether a strong mesodermal suture reaction or an epineural reaction was traumatic, infectious, or was caused by the irritation of the sulfonamide drugs.

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\* Fine crystalline sulfanilamide, sulfathiazole, and sulfadiazine powders were used in all the experiments.



The sulfonamide drugs did not interfere with the neurotization of an autogenous or homogenous graft, or the distal segment. However, in the homogenous graft series an heteromorphous neurotization of the graft was found in all of the sulfonamide-treated animals, whereas similar grafts in untreated animals showed in all instances some degree of isomorphous neurotization.

DISCUSSION—DR HOWARD C. NAFFZIGER, San Francisco, Calif. The work of Doctor Davis, and his associates, has indicated that for experimental wounds in animals the use of the sulfonamide drugs has effected a striking reduction in the incidence of infection. Their conclusion that, microscopically, the drug showed no significant effect on the regeneration of peripheral nerves is supported by Hinsey's laboratory experience. He believes that regeneration is neither accelerated nor retarded.

In Davis' animals, however, there were more adhesions in the wounds and more fibrosis. The degree of reaction varied with the particular drug. Their findings in peripheral nerve tissues *in vivo* agree with the results obtained by Saunders and Haymaker on the central nervous tissues of chicks in tissue culture. In both instances sulfadiazine headed the list as the greatest irritant, while sulfanilamide caused the least reaction.

Of the sodium salts, sulfadiazine is most toxic to growing tissue. The irritant and sclerosing effect of such drugs recalls to me four cases which I saw recently in England. In all of these sulfapyridine had been injected into the muscles of the posterior aspect of the thigh in the course of treatment of some infection. Sciatic paralysis ranging from severe to complete lesions resulted. In one sciatic nerve seen at operation the injection evidently had been into as well as about the nerve, resulting in a terrific production of scar tissue intraneurally and over a considerable distance along the nerve.

What should be our attitude toward early suture of the nerve in contaminated wounds, particularly those of warfare? In civilian life, divided nerves in incised wounds, or in lacerated wounds with little associated contusion, may, under favorable conditions, be sutured primarily. In battle wounds such conditions rarely prevail.

The length of time between injury and arrival at a hospital with suitable personnel and equipment will be many hours or days. Operations upon peripheral nerves are detailed and too time-consuming to be performed amid a rush of urgent cases. Associated injuries to bones, joints and soft tissues are the rule.

The loss of some length of nerve requires surgical ingenuity to approximate the ends. In the early stages the amount of resection required for the damaged ends may be debatable. The long incisions to mobilize the nerve and the extensive dissections to preserve the branches are not to be undertaken in contaminated wounds. The appropriate positions of bones and joints to permit approximation of the ends of the nerves may not be permitted by the exigencies of the associated injuries.

It is recommended, then, that, as a primary procedure at the time the wound is trimmed, the untrimmed ends of the nerve be approximated with a wire suture if possible. This prevents retraction and displacement and facilitates later identification at operation.

It has been the experience in this war that such divided nerves may then be suitably resected and sutured at an early date after healing of the wound. Experiments indicate that early suture favors the best regeneration, and clinical experience shows that the earlier function can be restored, the fewer will be the irreversible changes in muscles and joints, and the more complete will be the recovery.

In War I, the protracted sepsis in bone caused long delays in the repair of nerves and, even after healing, many weeks elapsed before the extensive operations required could be undertaken.

The experimental work of Doctor Davis, and his associates, and the clinical experiences in this war, in which there is less sepsis and more prompt healing of wounds, all

indicate that far earlier suture of nerves may be performed safely and that the use of sulfanilamide will not prejudice the result

Lebedenko has reported a large series of repairs of nerves, undertaken not later than two weeks after healing of the wound, with an insignificant percentage of infections

Early rather than primary repair of the nerve is the goal. With decreased infection, speedier healing of wounds and prompt repair, the results of surgery of the nerves may be expected to show great improvement

DR BYRON STOOKLEY, New York. The problem of nerve repair in war is one of meeting a nerve defect, and if there is anything we can do to prevent a nerve defect or at least minimize it, it will make for easier repair and a more complete return to function.

Doctor Davis has shown that with the use of sulfanilamide the nerve ends can be brought together earlier than they could otherwise. This means less retraction of the nerve ends, and as Doctor Naffziger said, if the new wire tantalum is used, which will not increase and retain the infection, then the retraction which takes place, and the fixation of the nerve in distal scar, can be overcome and at least minimized.

Therefore, the amount of nerve defect to be overcome at the time at which definitive repair can be made is efficiently lessened. Then an easier end-to-end suture is accomplished, and less demand for a nerve graft or other measures to bring about an end-to-end nerve suture is necessary.

Also, earlier repair can be accomplished, therefore less secondary changes in the periarticular structures, and degeneration in the muscles themselves. Consequently, any method which can be devised permitting end-to-end suture, easier, with less tension; and earlier, certainly offers a tremendous advantage over the type of injury which we saw in the last war, which as Doctor Naffziger said, permitted suture only after a relatively long delay.

With the advent of the sulfanilamides, not only applied locally but the possibility of taking these internally, certainly it would permit an earlier suture. It is interesting that Doctor Davis' work shows that the application of the drug locally interferes in no wise with the down-growth of the neuraxis and the repair of the nerve itself.

It is important to know that the drug does not increase the scar tissue within the nerve, and that the amount of increased scar found does not interfere with nerve regeneration.

DR FREDERICK L. RICHERT, San Francisco, Calif. Those who teach surgery would welcome the article in the United States Naval Medical Bulletin for February, 1944, on "Working Rules in the Field," by Comdr. Holman, with the assistance of Col. Oughterson, and a number of others.

They state, in chosen words, that with nerve injuries approximate the nerve ends with silk or wire, not to make a complete suture but to get the ends together, fix the joints in order to relax those nerves whose parts have been destroyed. They emphasize, in just a few paragraphs, the importance of the sulfonamides in the wounds, as Doctor Davis has pointed out, experimentally, and they emphasize from actual experience the necessity of approximating nerve ends, not suturing them but getting them into position so that at a subsequent time suture can be undertaken.

DR J. ALBERT KEY, St. Louis, Mo. This paper is important to me on account of the local use of sulfonamides. I saw Doctor Meleney this morning, and he said he still was not ashamed of the report which he read last year before this Association, and that everything he had heard since he read that report had tended to confirm the opinions expressed in it, namely, that sulfonamides do not reduce the incidence or the severity of wound infections when used locally.

I do not think he can see anything more convincing than this. I do not know what is the matter with New York City. It may be that new knowledge cannot penetrate the

catacombs, or it may be that facts get lost in that punch-card machine which they use, but it seems to me that everything I have seen or heard during the past year has confirmed my opinion that local sulfonamides should be used in wounds, and that this is further proof of that theory

DR FRANK L. MELENEY, New York I had not intended to discuss this paper, but I am willing to stand back of what I said to Doctor Key this morning

I think these are very interesting experiments that Doctor Davis has carried out I would like to point out, however, that the work has been done with cats, which are quite dissimilar to human beings in their reaction to infection They are usually much more resistant to infection than human beings, and yet he has found a high incidence of infection among his controls

Going over the figures, although the groups are small, I find that there is a consistency which is hard to get away from, and all of them (except one or two of the smaller groups) fulfill the requirements of the biostatisticians as to significance

I think, therefore, we will have to accept those figures, and his statement that the sulfonamides have definitely reduced the incidence of infection under the experimental conditions with which they have been used in his study

One of his statements, however, seems inconsistent, namely, that by 12 hours' time *all* of the wounds showed evidence of infection, and yet his figures for infection, both in the controls and in the treated cases, were considerably below 100 per cent Does Doctor Davis mean that the infection seen at 12 hours subsided spontaneously in certain of the control cases and in a higher number in the treated cases? It is in these groups in which no prophylactic drugs were used for 12 or 24 hours that the figures do not meet the full requirements of the biostatisticians as to significance

We will await with interest the reports from the front as to the efficacy of these drugs in human cases under combat conditions I have yet to see a large series of well-controlled figures which have come from the front which bear out Doctor Key's contention

Doctor Elliott Cutler has reported a small series of controlled cases with about 100 in each group, treated and nontreated, in which the incidence of infection was almost identical with our own figures, and showed no lowering of that incidence in drug-treated cases The reports that Capt Ferguson brought back were entirely without controls, and I am still going to maintain the accuracy of our observations until I can see some really convincing reports of well-controlled studies made by unprejudiced observers

I believe that the sulfonamides minimize the general spread of infection and thus lower the incidence of sepsis and death, but something interferes with their local action in the presence of damaged tissue so that they do not lower the incidence of local infections in wounds The problem of the prevention of local infection in wounds still remains to be solved An appraisal of penicillin is now under way

DR LOYAL DAVIS (closing) I find myself involved in a discussion between Doctors Meleney and Key about the use of the sulfonamides I want to make it clear in the beginning that I have simply attempted to present the results of experiments without bias

The following colored slides will show the gross effects of gunshot wounds of nerves at various intervals of surgical debridement following injury in which sulfanilamide, sulfathiazole, and sulfadiazine were used The point which we wish to make is that the best method of treatment for peripheral nerve injuries is an end-to-end suture performed as soon after injury as possible The effect of infection upon the results of peripheral nerve suture has been well established It is our opinion that these experiments give support to the view that if the sulfonamides are used at the time of debridement in gunshot injuries and if a peripheral nerve suture must be done several months later because of concomitant injuries to bone and soft tissue, then that wound so treated can be incised and the nerve sutured with less danger of lighting up an infection than if the sulfonamides had not been used Further, our position is that we have no microscopic evidence which

would show that regeneration of nerve fibers is interfered with by the sulfonamides. We are in entire disagreement with the opinion that the ideal method of treatment is to delay the suture. During that period of delay the effector mechanisms have so suffered, in that there will be an atrophy of muscle and fibrosis of joints, that even if nerve regeneration occurs the result will be poor. In the European Theatre of Operations we saw many cases of soft-tissue injury and fractures of bones complicated by peripheral nerve injuries which had been received in the North African campaign. When they arrived in England the wounds were healed, and in a large number of them the sulfonamides had been used at the time of the first surgical trimming of the wound. These wounds were incised, the nerves sutured after the bone had healed or skin grafts had been applied, without development of infection. We made it a rule to introduce sulfonamides locally into the wounds at the time the peripheral nerves were sutured. The emphasis, therefore, should be upon the practical surgical aspect of repairing a peripheral nerve injury as early as possible in order to obtain the best possible functional result.

# THIOURACIL IN THE PREPARATION OF THYROTOXIC PATIENTS FOR SURGERY\*

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EVERY PHYSICIAN AND SURGEON realizes that a method which can be used to lower the metabolism and improve the clinical condition of the thyrotoxic patient before operation is of the greatest importance. Those of us who have operated upon toxic goiters in the pre-iodine era recall very clearly the tremendous decrease in the mortality and morbidity of these cases after Henry S. Plummer taught us to prepare the patients with Lugol's iodine solution. In spite of the many benefits produced by iodine in the management of toxic goiter, however, everyone realizes that it has left much to be desired in many cases. Some patients do not have a return of their metabolism to normal and are still toxic after prolonged iodine treatment. Multiple-stage thyroidectomies are still necessary in a small percentage of cases regardless of the time or type of preoperative iodine treatment. With the recent addition of thiouracil† to the surgeon's armamentarium it would appear that we have at our command an agent which will reduce the toxic thyroid patients' metabolism to normal, will produce a remission of symptoms and a gain in weight before surgery is undertaken. In fact, it is distinctly possible that surgery will, in the near future, be unnecessary in many exophthalmic goiter patients.

The medical treatment of hyperthyroidism with thiouracil is the direct result of about three years of research work on goiter by pharmacologists, endocrinologists and clinicians, and is an outstanding example of the results that may accrue to medicine from the combined efforts of men in different fields who concentrate on a single problem. Physicians have known for many years that certain drugs would produce goiter, but not until 1941 were agents discovered which were goitrogenic in animals in spite of the administration of iodine. The hyperplasia and hypertrophy of the thyroid was apparently a work hypertrophy of the gland resulting from a cessation of the production of the thyroid hormone.

Kennedy and Purves<sup>1</sup> gave rats a diet of brassica (rape) seeds and produced goiters which histologically showed hyperplasia and hypertrophy of the acini with a complete absence of colloid. It is most important that these changes are not affected by iodine feeding. MacKenzie and MacKenzie<sup>2</sup> produced the same result by giving rats sulfonamides and thioureas. They concluded that these drugs produced a depressing influence on the functional activity of the thyroid and hence on the basal metabolism. Richter and Clisby,<sup>3</sup> also, in this same year reported similar experiences following the use of phenylthiourea.

\* Read before the American Surgical Association, May 3-4, 1944, Chicago, Ill.

† Thiouracil was supplied by Lederle Laboratories, Inc., Pearl River, N. Y.

Astwood,<sup>4</sup> in 1943, reported his studies on the chemical nature of 106 compounds which inhibit the function of the thyroid gland. He found that thiouracil was the most goitrogenic of these and was, therefore, probably the best drug to try in the clinical treatment of hyperthyroidism.

As a result of this and other experimental work, Astwood<sup>6</sup> first tried thiourea and later thiouracil for the treatment of three thyrotoxic patients. A fall in the basal metabolic rate occurred with a concomitant clinical improvement.

Williams and Bissell<sup>5</sup> next reported the use of thiouracil in nine more patients with hyperthyroidism, all of whom made similar clinical improvement and had a fall in their basal metabolic rate to normal. Still later, Williams and Clute<sup>7</sup> reported on the treatment with thiouracil of 72 patients with thyrotoxicosis, the majority of whom obtained a normal metabolic rate and a remission of the disease. It is apparent that thiouracil reduces the metabolism in hyperthyroidism to normal and produces a regression of the clinical symptoms of the disease.

We wish to report today, with especial reference to the surgical aspects, our experiences in treating 115 thyrotoxic patients with thiouracil only, or with thiouracil and thyroidectomy. Of these 115 patients, 81 were treated with thiouracil without surgery and 34 were treated with thiouracil and surgery. The results to date of the purely medical treatment of 50 cases have been reported by Williams and Clute.<sup>7</sup> In the great majority of cases the basal metabolism became normal and the toxic manifestations of the disease disappeared. When the protein-bound iodine of the plasma was studied it returned to normal after thiouracil therapy. Furthermore, all patients who have continued to take thiouracil have remained in a normal state.

In view of these observations, one naturally asks the question, "In what cases of hyperthyroidism should we perform a thyroidectomy, and in which ones can thiouracil be used with thyroidectomy?" This question cannot be adequately answered until a large number of cases treated with thiouracil have been followed for several years.

While awaiting further knowledge on this subject, it has been our plan to perform a thyroidectomy in the following situations: (1) In patients having a very large goiter, (2) in patients who live far away and cannot readily have frequent check-up examinations, (3) in patients who through ignorance or temperamental difficulties cannot be depended upon to carefully follow medical treatment, and (4) in the small number of cases who have undesirable reactions to thiouracil.

Thirty patients whom we have operated upon after thiouracil treatment have had typical uncomplicated exophthalmic goiter. Four cases have been of toxic adenomatous goiter. In this disease we believe that surgery is desirable, because there is a large mass of thyroid tissue in the neck, and also because of the chance of later substernal extension. We have not treated any single, discrete adenoma with thiouracil since we believe these cases must all be treated as premalignant lesions and removed. We have treated with thiouracil

15 patients with persistent or recurrent toxicity after thyroidectomy. Some of these subjects had been operated upon two or three times. All have responded satisfactorily to thiouracil, and, thus far, further surgery has not been necessary. This has been one of the most helpful uses of the drug that we have encountered.

The preoperative preparation of thyrotoxic patients with thiouracil is considerably more simple than it is with iodine. The average patient with hyperthyroidism, who is not seriously ill, is sent to the hospital for a general examination, a basal metabolism test, and for examination of the blood and urine. She is then started on thiouracil in doses of 0.2 Gm. three times a day at about eight-hour intervals. Within a day or two, depending somewhat on the patient's understanding of the problem, the great majority of the patients are sent home to take 0.6 or 0.4 Gm. of thiouracil a day. The patients are permitted to carry on with their usual work but are requested to return at intervals of two weeks for a check-up metabolism and blood test.

A careful follow-up is most important in these patients. They must not be lost sight of, because of the danger of possible complications from thiouracil. Some particularly uncooperative or ignorant patients have been kept on the ward because we feared that they would not return for follow-up studies or that they would not continue their treatment.

The length of time necessary for the metabolism to return to normal varies with the severity of the intoxication and probably even more with the type of gland present. A toxic patient who has taken iodine for a long time and has marked storage of colloid in the thyroid will respond to thiouracil much more slowly than a patient who has received no iodine. This seems to be related to the colloid content of the thyroid acini and particularly to the amount of thyroid hormone stored in the gland.

We treat patients with thiouracil for about five weeks preceding thyroidectomy. During this interval the patient is given thiamin chloride, 5 mg. daily, and urged to eat food containing much carbohydrate and protein.

When, from clinical examination and basal metabolism tests, the patient appears ready for surgery, she is admitted to the hospital. Usually, she is operated upon two days after entrance and returns home on the sixth or seventh postoperative day.

Exceptionally toxic cases and thyrocardiacs are kept in the hospital under immediate supervision until the patients are either well enough to go home to continue their preoperative treatment, or are ready for surgery. One unusually sick patient (Miss B. LaB.) with exophthalmic goiter may be briefly cited. Her thyroid gland was eight to ten times normal size. She entered the hospital on the verge of a gastro-intestinal crisis. She was given Lugol's solution, intravenous fluids and glucose, and after 17 days was taken to the operating room for ligation of the superior poles of the thyroid. Her pulse varied on the table between 160 and 180. No operation was undertaken. Thiouracil treatment was started and iodine gradually withdrawn within ten days. After three weeks she improved sufficiently so that a hemithyroidectomy was suc-

cessfully carried out. Six weeks later the metabolism had fallen to normal and the left lobe of the thyroid was removed. Thiouracil helped very greatly in this case when it became apparent that the patient would not respond to iodine. We believe, from later experiences, that longer preoperative treatment with thiouracil would probably have permitted a safe one-stage thyroidectomy.

Certain patients, perhaps ten per cent, have complications from thiouracil of sufficient degree to necessitate discontinuation of the drug. The most serious complication that has been reported is agranulocytosis. This appeared in one of Astwood's six early cases, and in one of Williams' and Clute's<sup>7</sup> cases. In one of these patients much larger doses of thiouracil were used than are now believed necessary. In some cases leukopenia has occurred, but with a decrease in dosage it has been possible to continue with the drug. The blood picture in each patient and especially their clinical condition must be followed carefully in order to avoid complications.

Several patients developed a morbilliform rash, with itching, which soon disappeared, although treatment was continued. Three patients developed urticaria. In one case this disappeared when thiouracil was stopped for a few days, and did not return when it was again started. In the two other patients the urticaria, joint pains and fever were so severe that the drug was stopped, iodine was given and surgery was undertaken. It is wise, we believe, to give thiouracil with great care to any patient known to have any allergic symptoms. Other milder reactions occurred from thiouracil, such as nausea and vomiting, but were never sufficiently severe to necessitate stopping the use of the drug.

The clinical improvement in these cases was usually noticeable in a few days after starting thiouracil unless the patients had been taking iodine for a long time. Iodized patients responded more slowly than others. The changes in the basal metabolic rate are best shown by the charts (Figs. 1, 2 and 3). The patients felt better and appeared improved days before their metabolism showed any major change.

During the period of preoperative preparation, usually, the thyroid gland became smaller and firmer. The active pulsations, thrills and bruits tended to disappear. In some cases the goiter seemed to become larger as treatment progressed, but this was unusual.

In most patients having a stare and a widened palpebral fissure, improvement in the eyes occurred as their general condition improved. In five cases there was marked edema of the lids with exophthalmos, such as one sees early in cases of malignant exophthalmos, and these patients became worse when thiouracil was used. In one, the ocular changes were so severe that corneal ulcers developed. Thyroid extract, 32 to 96 mg. per day, was used in conjunction with thiouracil, with improvement in all of the patients. In individuals showing manifestations of malignant exophthalmos, apparently, the minimal effective dose of thiouracil should be used to bring the metabolism to normal. Overtreatment may lead to an increase in the exophthalmos.

At the time of operation the thyroid gland in thiouracil-treated patients was quite firm, resembling the consistency of the untreated hyperplastic



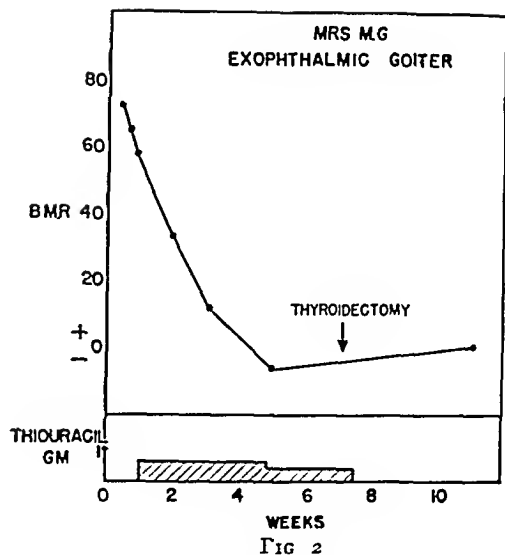
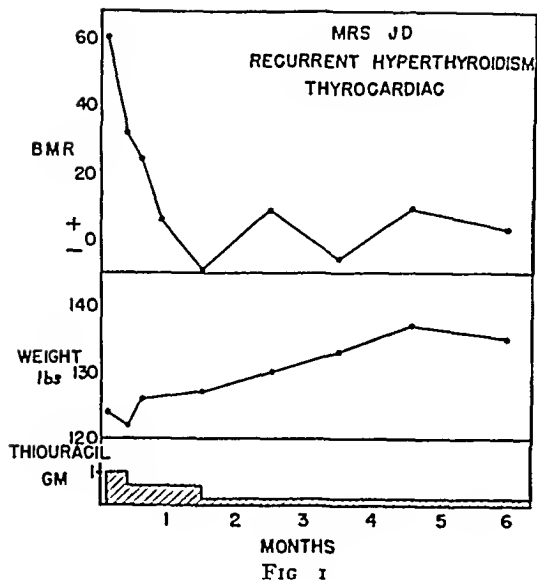


FIG 1—Chart of patient having hyperthyroidism and auricular fibrillation recurrent after thyroidectomy treated with thiouracil. No operation was performed. Note the maintenance of metabolism and weight at normal with small doses of thiouracil for over six months.

FIG 2—Chart showing the fall in basal metabolism of thyrotoxic patient prepared for surgery with thiouracil. The basal rate was normal one month after operation, with no further thiouracil treatment.

## PREOPERATIVE AND OPERATIVE COURSE

### MRS. C.W. AGE 68 SEVERE EXOPHTHALMIC GOITER

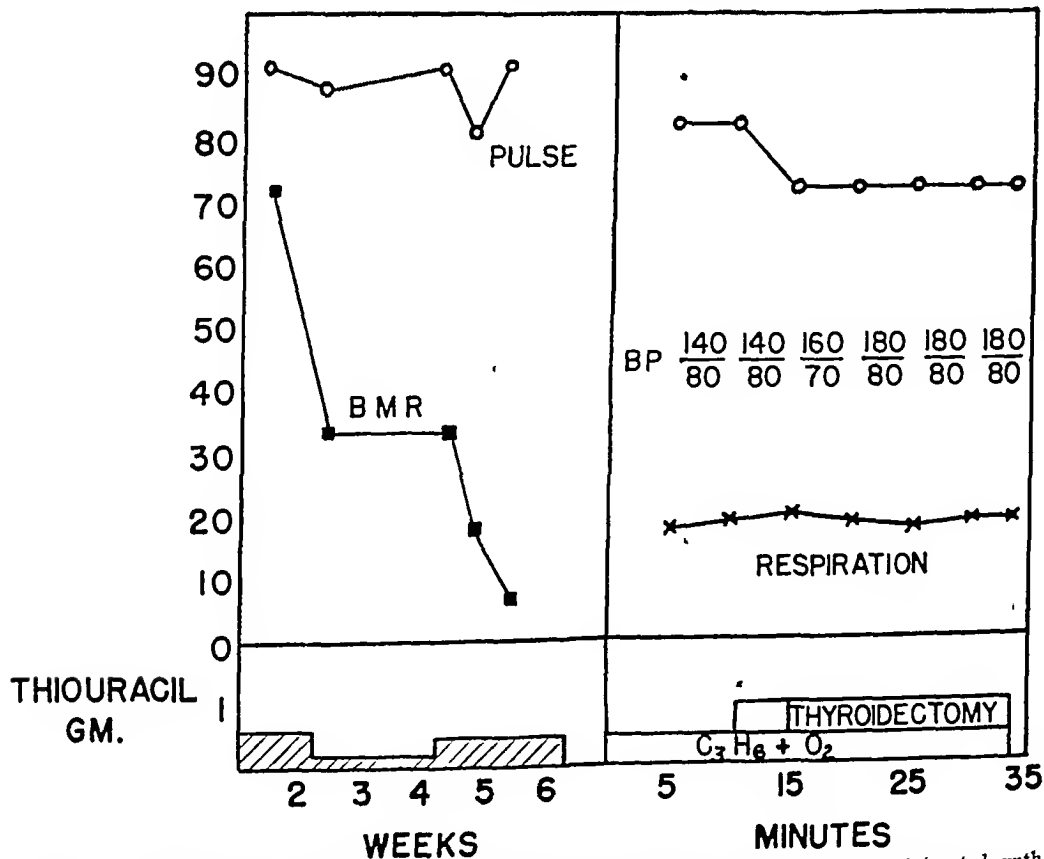


FIG 3—Combined chart of preoperative and operative course of thyrotoxic patient treated with thiouracil. Note the failure of the metabolism to fall from the second to fourth week with two small doses of the drug, and its rapid decline with increased dosage. Note the smooth operative course. The metabolism and pulse rate were normal seven days after operation.

thyroid The thyroid glands were not as vascular as they are in untreated cases, although the superior and inferior arteries were still of large caliber. The tissue surrounding the gland was at times densely adherent to it and cleavage planes were hard to establish. There was more bleeding encountered in some of the thiouracil-treated cases than in the iodine-treated cases, and it was necessary to spend quite a little extra time in its control.

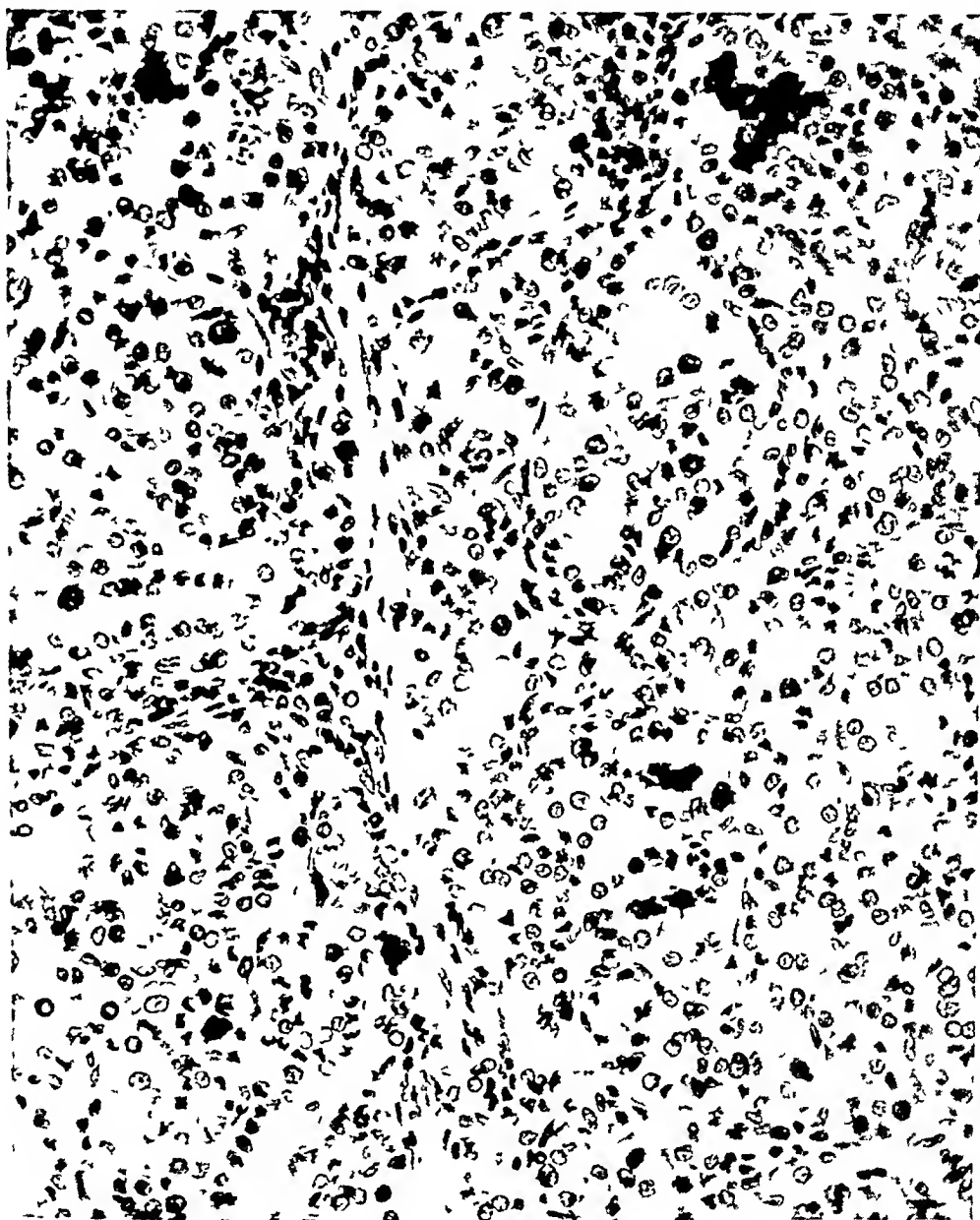


FIG. 4.—Histologic section of thyroid gland from patient with hyperthyroidism, after metabolism had been brought to normal with thiouracil. Note the small amount of colloid, the tall, columnar cells of the acini and the relatively few papillary projections.

Histologically (Fig. 4), the thiouracil-treated hyperplastic gland showed very little colloid. The cells of the acini were tall and columnar. Many of the acini were small and contracted—only a few showing papillary projections. There seemed to be an increase in interstitial tissue between the acini. There was little histologic difference in the glands of patients treated a few weeks

and patients treated many months. In patients who received both iodine and thiouracil there were definite increases in the colloid contents of the acini over those who had received no iodine.

The operative course in thyrotoxic patients treated for five or six weeks with thiouracil was remarkable only for its smoothness. They reacted, as would patients with a normal metabolism, to a moderate surgical procedure, with no marked changes in pulse or blood pressure. The postoperative course was equally smooth and uneventful. The nervousness, activation, and marked tachycardia, seen so often after operation upon patients whose metabolism has been brought close to normal by Lugol's solution, were entirely absent in these cases. The striking thing about the operative and postoperative course of thiouracil-treated cases was the absence of anything striking.

This was not true in the cases operated upon after only 10 or 14 days of thiouracil therapy. These patients were still toxic and, postoperatively, had the activation, tachycardia and fever, that would be expected. When treatment was continued for five weeks, or longer, and the metabolism had reached normal, postoperative reactions were negligible. Thiouracil was stopped four to six days after operation.

From the point of view of the anesthetist the induction and maintenance of these patients is quite like that of any patient with a normal metabolism. Dr. Eleanor B. Ferguson, who gave the anesthetics, found it necessary to use only average amounts of preoperative sedation. Toxic goiters treated with Lugol's solution require far heavier preoperative medication than do thiouracil-treated patients. Cyclopropane and oxygen has been the anesthetic of choice in all of our thiouracil-treated cases. Their course under anesthesia has been smooth and uneventful. From the viewpoint of anesthesia these patients no longer present a difficult or complicated problem.

We have to report one fatality in a thiouracil-treated thyrocardiac patient. This patient had had thyrotoxicosis for ten years, and had been treated throughout this period with iodine. She had had auricular fibrillation for over a year. She received thiouracil therapy for eight weeks. With this treatment her metabolism became normal, her clinical improvement was marked and her fibrillation ceased a few days before operation. She died about three hours after an uneventful thyroidectomy, probably from an embolus. Her pulse was 84 and her blood pressure 120/80, 15 minutes before death.

The late results after subtotal thyroidectomy in these cases have been very satisfactory. The metabolic rate has remained at normal in 33 cases. In one case a slight recurrence of toxicity has appeared, which was readily and completely controlled by small doses of thiouracil for a few weeks. In one case the basal rate had gone below normal for a few weeks, but with no special treatment has returned to normal within a few months. It is probable that occasional postoperative myxedema will be seen in patients who have considerable thyroiditis, associated with hyperplasia in their thyroid glands.

The four thyrocardiac patients have done exceptionally well. The absence of severe postoperative reactions has helped materially in making their final

recovery smooth and rapid. It is significant that nine thyrocardiac cases treated with thiouracil alone have done equally well.

The 15 patients with hyperthyroidism, recurrent or persistent after operation, have all been completely controlled with thiouracil, and are apparently well. No secondary operation has been necessary in any of this group.

#### CONCLUSIONS

In hyperthyroidism thiouracil reduces the basal metabolism to normal, with a corresponding decrease in the symptoms of the disease in almost all cases.

Which toxic goiter patients should be treated with surgery as well as thiouracil, and which cases can be managed with thiouracil alone, is a matter for continued study. A small percentage of patients are sensitive to thiouracil.

The operative and postoperative course of thyrotoxic patients prepared for surgery with thiouracil has been remarkably smooth and uneventful. The late results in the operated cases have been excellent.

Thiouracil is a valuable addition to our means for treating hyperthyroidism and for preparing patients with this condition for surgery.

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DISCUSSION—DR JOHN DEJ. PEMBERTON, Rochester, Minn. I feel that this Association is deeply indebted to Doctors Clute and Williams for presenting to us an account of their experience with thiouracil in the treatment of hyperthyroidism. Their series is the largest that has been published and the excellent results obtained speak for themselves.

The application by Astwood of the goitrogen, thiouracil, to the treatment of exophthalmic goiter was a brilliant piece of work. It has furnished a new tool for the study of thyroid physiology and has made an important addition to the available therapeutic agents. The ultimate status of thiouracil in the treatment of hyperthyroidism cannot, it seems to me, be clearly defined at present. It is obvious from the observations of Doctors Clute and Williams that it will play an important rôle in the preparation for surgical treatment of some patients with exophthalmic goiter. I agree with them that one of its most logical and important uses may be in the preoperative treatment of these patients who, because of the severity of hyperthyroidism, are unusually poor surgical risks. It also may be of value in cases of similarly high surgical risk because of complicating conditions added to severe hyperthyroidism. It seems doubtful to me if the present low

surgical mortality in cases of exophthalmic goiter of moderate or slight severity can be lowered by preparation with thiouracil rather than iodine, as the risk in such cases is already about as low as it is in cases of adenomatous goiter without hyperthyroidism

It seems desirable to emphasize some pathologic reactions which may accompany the use of thiouracil. Williams and Bissell have reported transient edema with depression of the carbon dioxide combining power of the plasma and elevation of the plasma chlorides. At the Mayo Clinic, we have noted a similar reaction in two cases in which thiouracil was administered because of severe recurrent exophthalmic goiter. In both cases, the reactions were so severe and so persistent that the administration of the drug had to be discontinued. In one of these cases the reaction was accompanied by swelling of the face, marked somnolence, muscular twitching, myoclonic spasms, incoherent slurred speech, vertigo and severe headache. This reaction occurred on each of three occasions when the drug was given. Although the basal metabolic rate fell to normal during the first period of treatment, after the administration of the drug was stopped, it rose to higher than previous levels. On two occasions the reaction occurred when the basal metabolic rate was between 0 and plus 10 per cent, and on the third occasion, when it was plus 70 per cent. This case, and others, will be reported in detail by Haines, Keating and Power.

We have seen no serious instance of agranulocytosis among the patients we have treated, but frequently have noted depressions of the leukocyte count. In all our cases with this reaction the leukocyte counts have risen to normal rapidly after the administration of the drug was discontinued temporarily.

I hope that the method of determining the concentration of the drug in the blood, which recently has been described by Williams, will be of help in determining the dose accurately and also in helping to anticipate some of the untoward reactions.

We have been hesitant, because of possible toxic effects of the drug, to use thiouracil as the sole therapeutic agent unless some complicating condition has made surgical treatment out of the question. In the few cases in which the patients were so treated, however, the results have been excellent up to date, but we feel that the patients should remain under observation during the entire period of treatment.

I look forward with great interest to the subsequent developments which thiouracil and related drugs will bring in the treatment of hyperthyroidism, and feel confident that its position will be one of importance.

DR ROSCOE R. GRAHAM, Toronto, Canada. We are indebted to Doctor Clute for his contribution to the treatment of thyroid disease with thiouracil.

Our series is very much smaller, but there have been three groups of cases of hyperthyroidism in which we felt that thiouracil therapy was of great value. First, in the differentiation of the group of cases where the problem is to determine whether we are dealing with a case of hyperthyroidism or an NCA syndrome. In our series, there are three cases in which the lack of response to thiouracil was the determining factor in establishing the diagnosis.

In the second group, we include the thyrocardiac patient who has suffered from circulatory failure. We are able, with the long-continued administration of thiouracil, to obtain before operation the maximum restoration of cardiovascular efficiency, which would not be possible with iodine therapy.

In the third group, we have patients suffering from an acute infection which has precipitated them into an acute hyperthyroid state. Again, the ability to carry on the prolonged administration of thiouracil permits the patient to recover from the disastrous effects of the infection, and operation can be undertaken at the optimum time.

Our group, headed by Dr. Walter R. Campbell, of the Department of Medicine, feels that with this small series we are unable to give any judgment as regards the possibility of avoiding operation by this management. We are very conscious, however, of the fact that agranulocytosis is a real hazard, and that the patients must be followed with

extreme care. It is encouraging that Doctor Clute gives us some hope that in their group this type of therapy may make it possible to avoid an operation permanently.

DR WARREN H. COLE, Chicago, Ill. I would like to report that we, likewise, have had favorable results in a very small series of cases, but I want to ask Doctor Clute one question regarding a type of reaction which we have had, and which he may have also encountered.

On two or three occasions, we have had an increase in symptoms when we gave thiouracil. The cardiac rate would increase up to 130 or 140, sweating, nervousness and other manifestations likewise increased. This flare-up in symptoms was so pronounced that we were reluctant to continue therapy with the drug, and discontinued it.

I would like to ask Doctor Clute if, with a smaller dose and continuing on through that initial period of two or three days, would the acute flare-up subside?

DR HOWARD M. CLUTE (closing). We cannot yet be certain as to the full value of thiouracil or of the permanency of its effects. Longer study of more cases treated by various men will give us a better insight of its true place in hyperthyroidism.

Certainly it is true, however, that in most toxic goiter cases thiouracil will reduce the metabolism to normal and make an almost inoperable case safely operable. In fact, in many of these cases after weeks of treatment, a new observer would doubt the diagnosis of thyrotoxicosis.

I have not seen the complication Doctor Cole speaks of. It seems to us safest to stop thiouracil at once when any severe complication arises, and revert to the use of iodine and surgery.

# THE RELATIONSHIP OF PROTEIN DEFICIENCY TO SURGICAL INFECTION\*

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THE CONSEQUENCES of a prolonged period of negative nitrogen balance in a surgical patient will depend upon the preoperative abundance of the protein reserves and the postoperative degree of their depletion<sup>1, 2, 3, 4, 5, 6</sup>. The significance of these reserves is even yet not fully realized despite the many recent studies indicating their dynamic relationship to the plasma proteins<sup>7, 8</sup>. Their amount and availability, however, constitute an important safety-factor in that, as a rule, a postoperative loss of nitrogen will be less serious, coming from abundant protein stores than from ones already depleted because of protracted debilitating disease. Moreover, if before operation upon a hypoproteinemic patient, the tissue-protein deficit can be at least partially corrected by the administration of high-quality proteins, the chances of survival should be considerably improved, provided that the mechanism responsible for blood protein synthesis has not been too severely damaged by the underlying pathologic process.

Nutritional emphasis upon protein metabolism in surgical conditions has usually centered around such problems as the relationship of albumin loss, regeneration and replacement, to surgical shock, burns, blood loss, nutritional edema, wound healing, liver impairment and anesthetic injury, and comparatively little consideration has been given to the function of proteins in the prevention or amelioration of postoperative infection. Yet infection is an ever-present surgical menace, and the best surgical technic may be of slight avail in a markedly hypoproteinemic patient. Although infection may develop even under conditions of good nutrition, it is more likely to become menacing or even lethal when basic immunologic mechanisms are seriously impaired. For example, infection tends to become especially threatening in association with marked malnutrition, starvation or wasting disease, or with such chronic debilitating diseases as malignancy (especially of the gastro-intestinal tract), nephritis, cirrhosis of the liver, ulcerative colitis and the like, where inanition is actually a prominent part of the pathologic picture<sup>9, 10</sup>.

Nevertheless, such patients may be operated upon with little realization by the surgeon that they are in the danger zone of severe hypoproteinemia.

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The experiments here reported were aided by grants from the John and Mary R. Markle Foundation, The National Livestock and Meat Board, and The Douglas Smith Foundation for Medical Research of the University of Chicago.

The following brief case history illustrates the latter point. A white female, 35 years of age, was operated upon for the removal of a carcinoma of the rectum. The operation, a combined abdomino-perineal resection, was performed under continuous spinal anesthesia. For 24 hours postoperatively the patient did well, then the temperature rose to 103.6° F. The posterior incision was opened and 5 Gm of sulfanilamide were placed in the wound, but despite this and various supportive measures she died on the third postoperative day. Necropsy revealed a generalized fibrinopurulent peritonitis. Immediately after death cardiac blood was taken for total protein estimation, this was 3.98 Gm per 100 Ml of serum. The history revealed that during the last two years she had lost 52 pounds in weight (159 pounds to 107 pounds). This severe loss of weight reemphasizes the fact stressed by Studley<sup>11</sup> that postoperative fatality rates tend to parallel the extent of the preoperative weight loss. Thus, Studley observed, in patients who had had a preoperative weight loss of more than 20 per cent of their normal weight, a postoperative fatality rate of over 30 per cent. In several of these patients, moreover, there was wound disruption and terminal pneumonia.

Pneumonia and other types of postoperative infection obviously develop because the primary defense barriers have failed to prevent bacterial penetration into the deeper tissues, the consequences of this failure must depend upon the combined and complementary activities of the forces of natural and acquired resistance and the ability of these forces to restrict further microbic growth and spread. An important question is, therefore, Do nutritional conditions influence these two types of resistance, and, if so, how?

It is to be expected that profound undernutrition and its concomitant depletion of the protein reserves should influence adversely the mechanisms of *natural* resistance, because a protracted period of protein deficiency leads eventually to marked atrophy of the liver, spleen, bone marrow and lymphoid tissues, and from these tissues most of the phagocytic cells originate. Moreover, inasmuch as protein is the basic material from which all tissues ultimately are constructed, the absence of protein stores necessary for further construction of leukocytic reserves might also reduce the continued production of phagocytes, particularly if protein synthesis were further impaired as a consequence of an advancing infection.

Of equal, if not greater, importance with respect to the harmful potentiality of many of the common pathogenic micro-organisms is *acquired* resistance. Acquired resistance differs from natural resistance mainly because of the antibody mechanism, and there is no reason to believe that antibody action is restricted to only particular kinds of infection. In fact, all pathogenic bacteria, once they have entered the tissues, are foreign proteins, hence they are antigenic stimulants, both locally and generally, of the antibody mechanism. Antibodies, collaborating with phagocytes, promote bacterial localization and thus help to bring incipient infections quickly to an end. It is only when antibodies are weakly formed, as, for example, when the antibody mechanism functions at a lowered level, that anti-



bacterial defense presumably must depend upon the latent potentialities of natural resistance. It would seem obvious, therefore, that the capacity of the antibody mechanism to respond effectively will determine both the extent and outcome of many types of infection, especially those which are otherwise imperfectly combatted by the forces of natural resistance.

In an effort to ascertain more precisely the nature and functions of the antibody mechanism we have been investigating its relationship to protein metabolism. The rôle of proteins in antibody production did not become apparent until after the demonstration that an antibody is actually a modified tissue protein, a molecule of globulin. This fact suggests, however, that the problem of antibody production is but a part of the larger problem of protein synthesis. In a series of publications we have presented evidence supporting this hypothesis and indicating that both the acquisition and retention of specific resistance may be determined largely by an adequate intake and utilization of dietary protein<sup>12, 13, 14</sup>

In the present paper additional evidence is submitted demonstrating that impairment of the antibody mechanism is one of the sequelae of protein undernutrition and that, when there is a lack of essential amino-acids normally required for the formation of serum globulins, antibody synthesis cannot proceed optimally, even if all the other known necessary dietary factors are present. Before presenting this evidence, however, a few of the reasons supporting our general hypothesis will be summarized briefly under three categories, *viz*, (1) the relationship of protein ingestion to the synthesis of normal globulin, (2) the relationship of protein ingestion to the synthesis of antibody globulin, and, (3) the relationship of protein deficiency to antibody synthesis and antibacterial resistance.

#### I THE RELATIONSHIP OF PROTEIN INGESTION TO THE SYNTHESIS OF NORMAL GLOBULIN

There is now good evidence that the fabrication of normal serum globulin is dependent upon the utilization of an adequate assortment of amino acids. For example, Whipple, and his associates, have shown "that globulin formation is directly dependent upon diet." Thus, in summarizing their experimental findings Madden and Whipple say<sup>8</sup> "the same 100 grams of beef serum which produced 38 grams of total plasma protein produced approximately 21 grams of albumin and 17 grams globulin. The addition of 100 grams bran flakes to a kidney basal diet results in the formation of about 12 grams albumin and 11 grams globulin. Since it has been shown that 100 grams casein will yield only 5 grams albumin and 7 grams globulin, and 100 grams gelatin 5 grams or less of each, it becomes apparent that, as measured by phasmapheresis, diet regulates globulin production equally as well as albumin."

The question remains, however. Does normal globulin originate only from nonessential amino-acids or does it require for its synthesis an adequate supply of several or even all of the *essential* amino-acids?

Chemical evidence concerning the structure of globulin should help to clarify the problem of its synthesis. Although complete amino-acid analyses of normal serum globulin are still lacking, there is evidence that it contains several of the amino-acids essential either for adequate growth of the white rat or for maintenance of nitrogen equilibrium in man. Improved methods of amino-acid analysis are necessary, however, before a final answer can be given. In the meantime we are utilizing a biologic method for the evaluation of protein quality which furnishes additional evidence that serum globulin probably contains all of the amino-acids essential for the growing rat<sup>15</sup>. The method consists in the daily ingestion by a hypoproteinemic adult white rat of known quantities of a test-protein, followed by the recording of weight recovery and serum protein regeneration at the end of a seven-day feeding period. The daily ration is adequate in calories, vitamins and salts, and has as its principal source of nitrogen the protein to be tested. An incomplete protein, such as gelatin, for example, will induce only slight serum protein regeneration and weight recovery, whereas a complete protein will cause both a marked serum protein regeneration and weight recovery. We have demonstrated by this method that purified globulins, of either bovine or human origin, and composed predominantly (over 90 per cent) of *gamma* globulin, are also high quality proteins. Thus in every instance in which they were tested, serum protein regeneration and weight recovery resulted practically as effectively as in animals fed the highest quality meat proteins.

## II THE RELATIONSHIP OF PROTEIN INGESTION TO ANTIBODY SYNTHESIS

All recent evidence has tended to strengthen the view that an antibody is but a specifically-modified molecule of normal globulin. An antibody molecule, therefore, in common with a normal globulin molecule, must be synthesized from amino-acids present in the food or stored and available in the protein reserves. But, inasmuch, as only a portion of the globulin fraction of normal serum contains antibody, more attention must be given to the antibody-containing portion. This so-called *gamma* fraction is characterized by its slow mobility in the Tiselius electrophoretic cell. Although it may not contain every type of antibody, at least several kinds have been demonstrated in immune serums from the horse, rabbit, rat, monkey and man. These antibodies, moreover, are interchangeable between species. Thus, rabbit and horse immune serums are suitable for antibacterial therapy in man, and human serum can react specifically with micro-organisms which infect lower animals. Furthermore, nutritional conditions which influence the fabrication of blood proteins, as for example, albumin, globulin and hemoglobin, act essentially alike in the dog, rat and man. There is reason to believe, therefore, that these basic mechanisms of protein synthesis function similarly in all mammalian species. Furthermore, the concentration of the globulin fraction in man tends to rise in infections characterized by hyperproteinemia, such as tuberculosis, syphilis, lymphogranuloma, sarcoid, leishmaniasis,

rheumatoid arthritis, lupus erythematosus, etc. In some instances, also, there is a concomitant increase in the amount of *gamma* globulin.

Normal human serum contains around 25 mg per Ml of globulin, of this, approximately 8 mg, or about one-third, may be *gamma* globulin.<sup>16</sup> It is in this one-third of the globulin fraction, therefore, that the antibodies are found. Furthermore, inasmuch as the rise and fall in concentration of antibody globulin may parallel that of total globulin, a hypoglobulinemia may be accompanied by a corresponding decline in the amount of *gamma* globulin. Conversely, however, hyperglobulinemia does not necessitate an increase in the *gamma* fraction or in its antibody-containing portion, because during the time of the rise, as for example, during the process of reversal of the albumin-globulin ratio, antigenic stimulation might be absent. In hyperimmune animals, however, as much as 35 per cent of the total globulin fraction has been found to be antibody globulin. It should be borne in mind also, that inasmuch as more than two-thirds of the total globulin fraction presumably has no relationship to antibody content, concentration of this fraction in the blood (*alpha* and *beta* globulin) might rise and yet have no relationship whatever to a decreased content of antibody *gamma* globulin or to depletion of the *gamma* globulin reserves.

### III THE RELATIONSHIP OF PROTEIN DEFICIENCY TO ANTIBODY SYNTHESIS AND TO ACQUIRED RESISTANCE TO INFECTION

If our interpretation of the foregoing facts is correct, protein inadequacy and concomitant depletion of the protein reserves should lead in time to impairment of the capacity of a protein-depleted animal or patient to fabricate *gamma* globulin. This we have shown to be true for the production of agglutinins, precipitins and hemolysins, both in rabbits and white rats. Such animals also react less effectively against certain spontaneous and induced infections.

Our experiments with rabbits indicated that severe protein deficiency, in association with general undernutrition, lowered markedly the levels of serum protein and hemoglobin concentration and induced a significant decrease both in the rate and quantity of antibody output. In order to ascertain more precisely the effects of protein depletion upon the antibody-forming mechanism, experiments utilizing the hypoproteinemic adult white rat were performed in animals, which, during the period of protein depletion, were fed a diet presumably adequate in other nutritional elements. When the rats had become markedly hypoproteinemic they were injected intravenously with antigen in order to determine the output of antibody. As controls, rats which during the period of protein depletion in the first group, had been fed a diet identical in every respect except for the presence of 22 per cent casein, were similarly injected.

The compositions of the rations fed to the two groups of animals were as follows

	(Per 100 Gm of Ration)	
	Ration 3E†	Ration 3C‡
Ground fresh carrots	30 Gm	30 Gm
Ruffex	5 Gm	5 Gm.
Lard	4 Gm	4 Gm
Cornstarch	44 Gm	22 Gm
Casein (vit test Smaco)	none	22 Gm
Osborne & Mendel salt mixture*	4 Gm	4 Gm
Dried Brewer's yeast (Mead Johnson)	2 Gm	2 Gm
Liver concentrate (Wilson & Co 20 1)†	1 Gm	1 Gm
Water	10 Ml	10 Ml
Calcium pantothenate	200 gamma	200 gamma
Pyridoxine HCl	200 gamma	200 gamma
Riboflavin	500 gamma	500 gamma
Choline chloride	100 mg	100 mg
Oleum percomorphum		
—vitamin A	200 USP units	200 USP units
—vitamin D	29 USP units	29 USP units

\* Hawk and Osers modification plus 1 Gm each of copper sulphate and zinc chloride added to the trace elements

†Generously supplied by the pharmaceutical laboratories of Wilson and Company, Chicago

‡Ration 3E contained approximately 2 per cent of protein in contrast to the 22 per cent of case in ration 3C Both rations contained two rich sources of B complex vitamins in addition to those present in the raw carrots and added as synthetic vitamins

The rats (Sprague-Dawley strain) were kept in large wire-mesh cages with wire bottoms, six animals per cage, throughout the experiment each rat received 20 grams of ration per day Consumption was good in both groups, falling off only in the animals on the low-protein group as they lost weight Water was given *ad libitum* together with 20 grams of leaf lettuce per rat per week

Table I summarizes the essential data with respect to initial weights, length of dietary periods, weight gains or losses, and concentrations of serum protein and hemoglobin at the time of injection of the antigen.

TABLE I

Exp No	No of Animals	Av Initial Wts (Gm )	Diets	Diet Period	Av Values at Time of Antigen Injection		
					Wt Loss or Gain (Gm )	Sérum Protein Gm % Concentration	Hb Gm %
1	12	304	3C	5 mos	+ 23	6 68	15 1
	12	316	3E	5 mos	—119	4 24	10 2
2	12	307	3C	6 mos	+ 49	6 71	14 3
	12	315	3E	6 mos	—151	4 39	7 5

Blood for the various determinations was obtained from a tail vein in 1 Ml amounts Serum protein concentrations were determined routinely by the specific gravity method of Baibour and Hamilton<sup>17</sup> This method, in our experience, has checked consistently ( $\pm 0.2$ ) with the micro-Kjeldahl method of Ma and Zuazaga<sup>18</sup> and the direct biuret method of Kingsley<sup>19</sup> It affords a relatively simple and rapid way of determining serum protein concentrations in small quantities of serum or plasma Hemoglobin concentrations were determined by means of the Dick-Stevens photo-electric hemoglobinometer<sup>20</sup>

After the above data had been obtained all rats were injected simultaneously in a tail vein with 1 MI of a 0.25 per cent suspension of washed sheep's erythrocytes. The cells were always centrifuged at the same speed and time at the last washing before preparation of the suspension either for injection of hemolysin titration. A sample of blood serum taken from each animal before the antigen was injected was titrated for evidence of naturally-occurring hemolysin, starting at a serum dilution of 1-60, only an occasional serum contained hemolysin and none showed complete hemolysis at this dilution of serum.

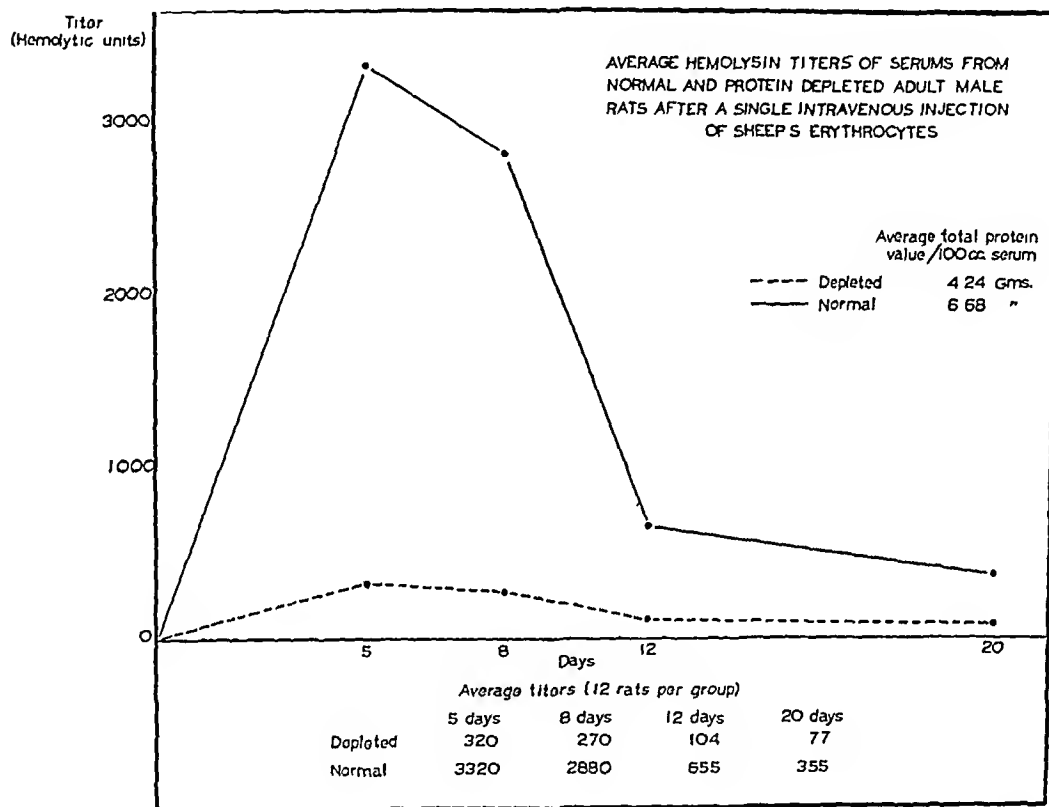


CHART I

For the hemolysin titrations a method used originally by Hektoen<sup>21</sup> was employed, modified in that a 2 per cent suspension of washed sheep's erythrocytes in 0.85 per cent salt solution (0.2 MI) was mixed with 0.3 MI of appropriately diluted inactivated immune serum and from 0.1 to 0.15 MI of a 1-6 dilution of pooled fresh guinea-pig serum. The complement in the guinea-pig serum was always titrated in association with the pooled inactivated serums from three protein-deficient rats which had been injected intravenously with sheep's erythrocytes, from one and one-half to two units were used in the final titrations, the titrations to determine hemolytic activity were all done simultaneously, using the double dilution method at a beginning serum dilution of 1-60. The hemolytic titer was taken as the highest dilution of serum showing complete hemolysis, all titers being recorded after incuba-

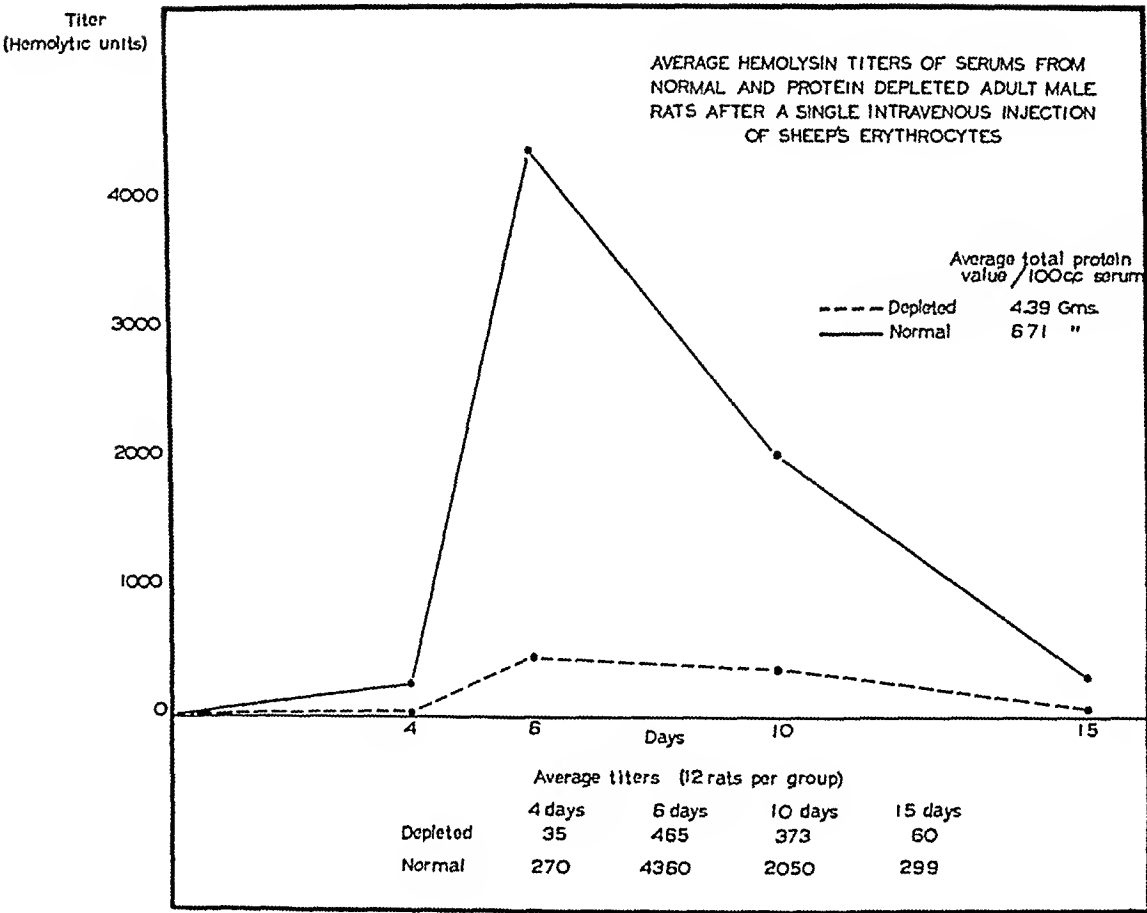


CHART II

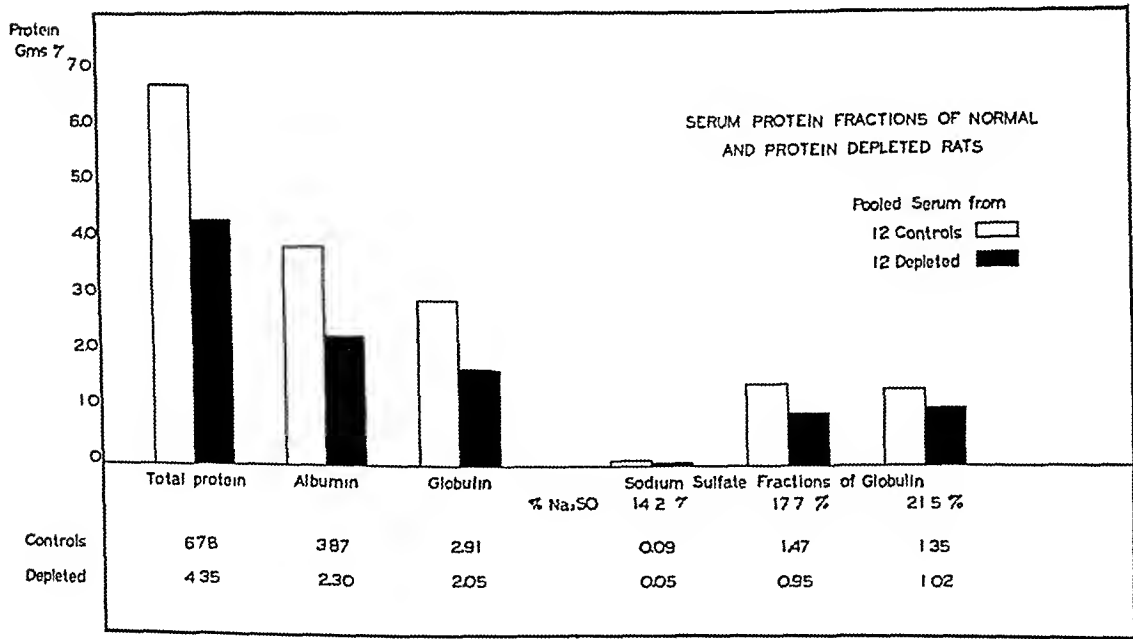


CHART III

tion at 37° C in a water bath for two hours and storage overnight in a refrigerator at approximately 4° C

The results for two groups of animals are shown graphically in Charts 1 and 2, where it is seen that at the peak of antibody-output (6-8 days) the average hemolysin titers for the normal sera were approximately ten times higher than those from the protein-depleted rats, the differences are also striking at the later periods. In other words, the animals with abundant protein reserves and an adequate protein intake were able, on the average to fabricate approximately ten times as much antibody as were those with depleted reserves and the low-protein diet continued during the period of antibody production

Besides demonstrating a decreased capacity to fabricate antibody, the protein-depleted rats also manifested a definitely increased tendency to develop

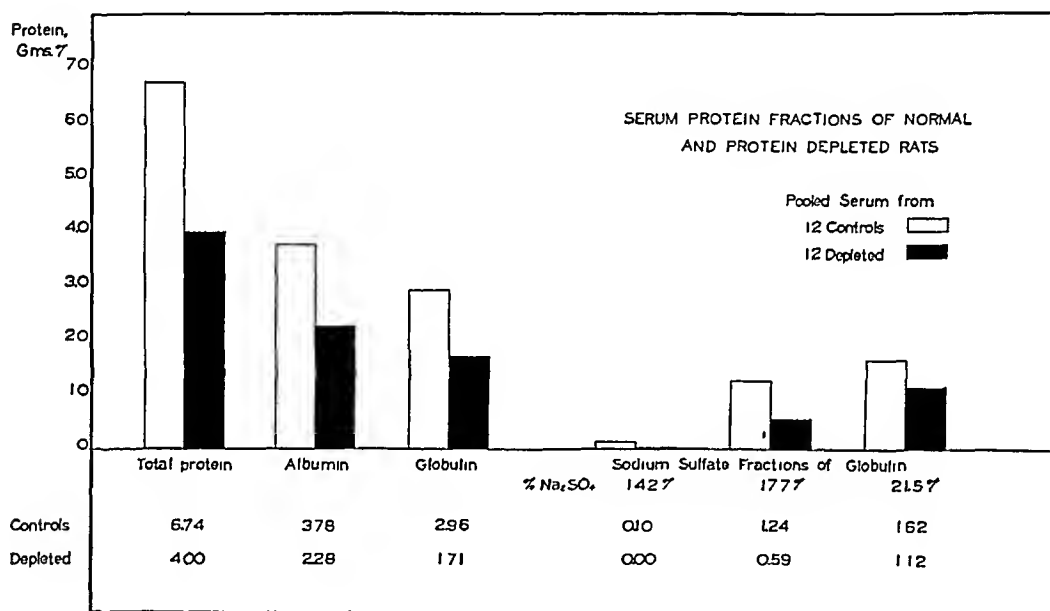


CHART IV

spontaneous infection. For example, in the first experiment three of the twelve hypoproteinemic rats died during the following three weeks, at the end of this period, moreover, four others exhibited varying degrees of chronic abscessive pneumonia. In the second experiment nine of the twelve hypoproteinemic rats showed, when sacrificed, a chronic abscessive pneumonia. In contrast, none of the control rats in either group showed any gross evidence of pulmonary infection.

In addition to testing antibody titers the serums were also pooled in order to ascertain the comparative concentrations of albumin and the various globulin fractions in each group. The results are shown graphically in Charts 3 and 4.

*Procedures*—Serums from 12 rats of each group were pooled (0.1 MI per

rat) and a total protein determination made on 0.1 Ml in duplicate (biuret method)<sup>19</sup> The remaining portions of serum were then mixed with various concentrations of sodium sulfate according to the procedure of Howe<sup>22, 23</sup> Serum (0.3 Ml) was added to 4.5 Ml of a solution of sodium sulfate to give a final sulfate concentration of 14.2 per cent, 17.7 per cent and 21.5 per cent. After mixing, the tubes were allowed to stand overnight at room temperature (around 25° C). Next day the mixtures were centrifuged and residual protein determined in the supernates. From the results shown in Charts 3 and 4, it is evident that the rats on the low protein diet developed both hypoalbuminemia and hypoglobulinemia, with diminished concentration of all three globulin fractions, *viz*, euglobulin, and pseudoglobulins I and II.

DISCUSSION —We have demonstrated by both immunologic and chemical methods that in the blood serums of protein-deficient rats there is a lowered concentration of antibody globulin and of three globulin fractions. This indicates definitely the adverse action of protein deficiency upon protein reserves and their capacity to generate serum proteins. In many surgical conditions there is also both a preoperative and a postoperative loss of various serum protein fractions, as into exudates, from hemorrhage or through the kidneys. Furthermore, undernutrition caused by an inadequate intake, absorption or utilization of high-quality protein may also lead to a steady depletion of the tissue protein reserves, both before and after operation. This loss of tissue proteins may finally become critical if and when a potentially pathogenic micro-organism enters tissues unprepared to mobilize the forces of acquired resistance.

It is obvious, moreover, from these experiments, that reliance upon the so-called albumin-globulin ratio for the determination of the state of the tissue protein reserves is inadequate. We need to know not only whether the globulins are in a lowered concentration, but particularly whether there is a diminished concentration of the *gamma* globulin fraction. If the total serum globulin concentration is low, the *gamma* fraction will also probably be low, if, on the other hand, the serum globulin is present in normal or elevated concentration, either condition may be due to an increased concentration of *alpha* or *beta* globulin and reveal nothing about the concentration of *gamma* globulin. What is actually needed is a quantitative clinical method for determining the concentration of *gamma* globulin.

In the absence of such a method dependence must be placed upon clinical procedures, such as evaluation of the extent of the preoperative weight loss and total serum protein determinations. The latter must be done, however, after proper attention to the problem of rehydration of the patient's tissues.

✓ If the total serum protein concentration is found to be less than 5 grams per 100 Ml of serum, preoperative protein repletion should be attempted, if possible, either by ingestion or intravenous administration of high quality proteins, in order both to reduce the tissue protein deficit and to build up a backlog of protein reserves available for antibody production in the



event of a developing infection. For unless the antibody globulin reserves can be replenished through the utilization of a proper supply of essential amino-acids, infection cannot be effectively combated through the intermediation of the antibody mechanism.

Since *gamma* globulin is a high quality protein, it presumably contains many if not most of the essential amino-acids. For its synthesis, therefore, it is necessary to provide an abundance of essential amino-acids in the protein reserves or in the daily food. In experiments to be reported later we have demonstrated that, when high quality proteins are fed to hypoglobulinemic rats, the animals quickly regenerate immune globulin, as evidenced by the rapid recovery of their capacity to produce specific antibody. This does not happen, however, when poor-quality proteins are fed. The inference seems warranted, therefore, that in patients with depleted globulin reserves, repletion necessitates the ingestion or intravenous administration of proteins containing all of the essential amino-acids. The further effects will obviously depend upon the patient's ability to convert these amino-acids into tissue proteins, including antibodies.

#### SUMMARY AND CONCLUSIONS

Both the frequency and severity of postoperative infection depend largely upon the capacity of the individual to mobilize the protective forces of natural and acquired resistance. These forces are dependent, basically, upon protein metabolism, acting through the agency of amino-acids ingested in the food or readily available in the tissue protein reserves. Attention has been directed in the present discussion to the rôle of the blood and tissue globulins, especially the *gamma* globulin fraction, in the mechanism of acquired resistance, and to their origin from dietary amino-acids. Evidence has been presented indicating that, to the extent that protein deficiency leads to depression of the capacity of certain tissues to fabricate antibody globulin, the potential ability to elaborate specific antibodies is concomitantly impaired. The implications of such protein depletion with respect to starvation, particularly in surgical patients, are discussed.

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EMERGENCY GASTRECTOMY FOR ACUTE PERFORATION  
OF  
CARCINOMA OF THE STOMACH, WITH DIFFUSE SOILING  
OF THE FREE PERITONEAL CAVITY\*

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ACUTE PERFORATION OF CARCINOMA of the stomach into the free peritoneal cavity occurs so infrequently that few surgeons have had an opportunity to observe more than a single case. Invariably the encounter has been unanticipated. The abdomen has been opened upon a diagnosis of perforated peptic ulcer and the situation managed without the advantage of precedent in personal experience and probably in most instances without knowledge of the experience of others. Furthermore, since many of the perforations occur in small ulcerating carcinomas without gross metastases there has been failure in many instances to recognize the malignant character of the perforated ulcer, with the result that it has been managed as a benign lesion by simple closure of the perforation. Incidentally, this fallacy can be prevented by the routine practice of immediate pathologic examination of a biopsy from the border of all perforations encountered on the gastric side of the pyloric sphincter.

Any surgical treatment short of resection in the resectable cases is of doubtful value. Granting the desirability of resection, the question arises, should resection be performed as an emergency gastrectomy in the presence of diffuse soiling of the peritoneum or should it be reserved for a secondary operation contingent upon recovery from the primary operation of simple closure of the perforation.

Because this and other questions relating to this entity can be answered only by the accumulation of many isolated individual experiences, it seemed justifiable to record our experience with a single case and to add a statistical compilation of the reported cases to date.

**Case Report**—J S, Negro, male, age 49, was readmitted to the hospital department of the Union Pacific Railroad at 2 P M, December 6, 1942, writhing with generalized abdominal pain. The onset had been sudden four hours previously with severe pain in the epigastrium which diffused rapidly throughout the abdomen and then to the top of both shoulders. He had vomited a small amount of clear fluid soon after the onset.

He related that for one year he had had burning and gaseous distress in the epigastrium which came on two or three hours after meals and during the night, and that this distress was relieved by the ingestion of food or alkalis.

On his first admission, three months previously, a diagnosis of duodenal ulcer

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had been made upon the basis of a persistent deformity of the duodenal cap, with a ten per cent five-hour gastric retention, normal free and total acids, and the repeated presence of occult blood in the stools. After ten days hospitalization on an ulcer regimen he was totally, if only temporarily, relieved of symptoms.

The patient presented the classical signs of perforated ulcer, with the confirmatory roentgenographic evidence of free gas in the peritoneal cavity.

Operation was performed one hour after admission and five hours after onset of symptoms. Upon opening the peritoneal cavity there was an escape of much gas and "dishwater" fluid. The latter seeped from a diffuse distribution throughout the abdomen. The stomach, delivered into the wound, presented a small perforation on the superior aspect of the anterior wall approximately three inches proximal to the pylorus. Palpation revealed that the perforation was located in the center of a crater the size of a silver dollar which had a wide, hard elevated border confluent inferiorly with a similar border surrounding a smaller crater. Except for a few questionable lymph nodes along the lesser curvature there was no evidence of metastases. A small piece of tissue was excised from the edge of the perforation and examined in frozen-section. The pathologist returned a report of adenocarcinoma.

Confronted with a situation regarding which we had no knowledge, we reasoned that healing of a perforation through carcinomatous tissue would be unlikely and, since the lesion appeared to be a very favorable one for resection, an immediate subtotal gastrectomy, even in the presence of a soiled peritoneal cavity, seemed a justifiable and logical procedure. Consequently, a resection of the Polya-Balfour type was performed. Five grams of sulfanilamide crystals were distributed over the peritoneal surfaces, and the peritoneal cavity closed without drainage. The wound in the abdominal wall was washed copiously with salt solution, dusted with sulfanilamide crystals and drained.

*Pathologic Examination*—"A large segment of stomach, with attached mesentery. Eight centimeters from the pylorus there is a crater, which measures four and one-half centimeters in diameter, with a central perforation the size of the head of a match. Adjacent is a smaller crater measuring one and one-half centimeters in diameter. Both are surrounded by induration which disrupts the normal mucosal pattern. On the serosal surface there are thickening and fibrinous changes over the area of perforation. No nodes were found in the attached tissue. Sections from the borders of the crater show well-formed glands with well-differentiated cells containing hyperchromatic nuclei. There is occasional mitosis, also invasion of the muscularis. *Pathologic Diagnosis* Perforated ulcerating adenocarcinoma of the stomach, Grade II, with no metastases to nodes of the attached mesentery."

The immediate convalescence was entirely uneventful. Ten days following dismissal from the hospital the patient developed a fever and a pleuritic type of pain at the base of the right chest. He was readmitted to the hospital and a small right subphrenic abscess drained.

He returned to work in four months and has remained free of symptoms and apparently well, now one year and four months following operation.

In this case there was the advantage of a record of complete gastrointestinal studies three months prior to perforation. The normal acidity of the gastric contents which soiled the peritoneal cavity was probably an important factor in preventing a bacterial peritonitis. The typical ulcer history of one year's duration, in addition to normal acidity, raises the question whether the carcinoma was the sole and primary lesion or had its origin in a preexistent benign ulcer. The low grade of the tumor and the absence of demonstrable metastases made for a very favorable prognosis.

One hundred and twenty years ago Laennec recorded in his case book an instance of perforation of carcinoma of the stomach with peritonitis. Since then the case reports which have appeared in the literature have been collected periodically. In 1934, Arid reviewed previous analyses and assembled 71 reported cases. To these he added one of his own, and seven other cases treated in the Royal Infirmary at Edinburgh.

From a review of the literature since 1934, the writers collected an additional 138 cases in which the diagnosis had been established at operation or postmortem examination. In approximately one-half of these cases no operation had been performed.

The combined series of 217 cases gives an erroneous conception of the incidence of perforation. Unquestionably, only a few of the total number of cases have been reported. A more accurate impression can be gained from several available surveys of case records and autopsy reports. In these the incidence varies from 2.8 to 60 per cent, as follows: Brinton, 21 perforations in a total series of 507 cases of carcinoma of the stomach; Ditrich, seven in 110; Lange, 12 in 210; Tornow, nine in 255; Jaissou, six in 135; McNealy and Hedin, 116 in 3,289; and Caseburg, seven in 247.

In only seven of the 217 cases was it alleged that a correct diagnosis had been made prior to operation or postmortem examination. More astonishing was the failure, in the majority of instances, to recognize at operation that perforation had occurred in a carcinomatous crater instead of a benign peptic ulcer. As stated previously, this fallacy can be prevented by routine practice of frozen-section biopsy from the area of perforation in all gastric perforations. The failure to recognize the presence of the carcinoma suggests that the majority of carcinomas which perforate are small and relatively confined lesions, presumably suitable for resection. This premise has been borne out at the autopsy table. In these cases there is, therefore, the possibility of considerable salvage of life.

From a study of 46 case histories collected from the literature, Chavannaz and Radoievitich distinguished four clinical types: (1) Cases with a sudden onset of severe epigastric pain and manifesting the typical signs of a perforated peptic ulcer, this preceded by a long or short history of dyspepsia; (2) cases differing from (1) only in respect to absence of previous dyspepsia; (3) cases with an insidious onset exhibiting signs of a gradually progressive peritonitis; and (4) cases that die of peritonitis and at no time have symptoms to direct attention to the abdomen. About 70 per cent of the cases are types (1) and (2).

Records of gastric analyses were presented in eight of the histories reviewed by Arid, and in 15 of our collection. It is interesting that achlorhydria was present in only four cases, and that in most of the cases the acids were normal or excessive. This finding has been offered as further evidence that carcinomas which arise in the presence of normal acids are ulcer-carcinomas, and arise in preexistent peptic ulcers. It can also be reasoned that a penetrating peptic ulcer can develop in a carcinoma. The break in the mucosa initiated by

the new growth exposes the underlying tissue to the digestive action of the gastric secretions which may rapidly penetrate the wall and be responsible for the perforation. Irrespective of this academic question, certain facts stand out. As in our case, the cases with normal and high acids had long histories of dyspepsia usually typical of ulcer and upon perforation presented a clinical picture and pursued a course identical with that of perforated peptic ulcer.

Too little data is available to determine definitely the influence of achlorhydria. Such as there is, suggests that carcinomas, in the absence of acid, perforate as a result of necrosis rather than ulceration and the perforation is likely to be relatively painless and silent, or if sudden and painful then rapidly fatal from septic peritonitis.

The two important problems relating to perforated carcinomas of the stomach are, first, recognition of the carcinoma by routine biopsy, and, second, operative management. In approximately 50 per cent of cases a hopelessly incurable situation exists as a result of advanced peritonitis from septic soiling or delayed intervention or because the tumor is not resectable.

There is no question about the desirability of resection of resectable lesions, only a question of when it should be undertaken. In an endeavor to answer this question the results of the various methods of management used in the 115 operated cases of the collected series are as follows (Table I).

TABLE I  
RESULTS OF OPERATIVE PROCEDURES IN 115 CASES OF PERFORATED GASTRIC CARCINOMA

Operative Procedure	Recovered	Hospital Deaths
Drainage alone	3	15
Simple closure (with or without drainage)	9	34
Local excision with simple closure	2	4
Simple closure and gastro-enterostomy	7	16
Simple closure and jejunostomy	0	2
Jejunostomy alone	0	2
Primary simple closure and resection at subsequent operation		
(1) Planned	1	1
(2) Corrected*	2	2
Primary resection	13	2
	<hr/> 37	<hr/> 78

\* Perforation at primary operation misdiagnosed peptic ulcer and proved malignant by subsequent developments and studies.

A mortality of 80 per cent following simple closure of perforations is understandable. Several reports contained remarks about the difficulty in obtaining satisfactory closure. Because sutures cut through the rigid and friable carcinomatous tissue, a few surgeons had to resort to suturing a patch of omentum over the perforation. In most instances postmortem examination showed failure of healing, with continued or subsequent leakage. This very considerable and inescapable hazard vitiates the theoretic advantage of the staged-method of management—that is emergency closure of the perforation by suture followed some days or weeks later by gastrectomy. In our collected series, six of the cases which recovered following primary closure were subsequently subjected to gastrectomy. Only three of them, or 50 per cent, sur-

vived In two cases, the two-stage procedure had been planned at the initial operation, in four, the perforation had been closed in each instance upon the assumption that it was a perforated peptic ulcer After subsequent events and studies had proven these cases to be perforated carcinomas, resection was performed Furthermore, it is apparent from the histories that several additional cases which failed to survive simple closure had resectable lesions which probably would have been resected at a second operation

For comparison with this record of two-stage management, there are available in the literature the records of 15 primary resections, including our case, with the incredible result of only two fatalities, a mortality of only 13 per cent

In the series of cases collected by Aird there were seven primary gastrectomies, with no mortality McNealy and Hedin reported seven primary gastrectomies, with two fatalities, in a group of cases collected by them from the records of Cook County and Wesley Memorial Hospitals Both authors expressed the opinion that the superior results from primary gastric resection should be accepted with certain reservations They believed that it was reasonable to assume that cases subjected to gastrectomy were in the most favorable general condition, and that there is probably a tendency to report solitary successes and for the failures to be absent from the literature These intangible factors in the available data make a comparative estimate of the merits of the single- and two-stage operations impossible However, it is our opinion that the hazard of a gastrectomy in the presence of a diffusely soiled peritoneal cavity has been grossly overestimated, and the hazard of leakage from a sutured perforation in carcinomatous tissue much underestimated

#### CONCLUSIONS

- 1 Acute perforation into the free peritoneal cavity is an infrequent but not a rare complication of carcinoma of the stomach
- 2 Approximately 50 per cent of carcinomas which perforate are otherwise resectable upon the basis of generally accepted standards
- 3 In many perforated carcinomas there has been failure at operation to recognize the presence of a neoplasm This fallacy can be prevented by routine frozen-section examination of a biopsy from the edge of all gastric perforations
- 4 For resectable lesions emergency primary gastrectomy is the operation of choice

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# COMPLICATIONS AND MORTALITY IN SUBTOTAL GASTRECTOMY FOR DUODENAL ULCER<sup>‡</sup>

## REPORT ON A TWO-STAGE PROCEDURE

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IN 1940, one of us saw in consultation on the Medical Ward at the Massachusetts General Hospital a 62-year-old man who had been admitted to the hospital because of a massive hemorrhage from a duodenal ulcer. His bleeding stopped and an elective subtotal resection of his stomach was performed six weeks later. He died on the eighth postoperative day from a general peritonitis. At autopsy, the infection was found to arise at the duodenal stump, although no actual perforation could be demonstrated.

One year later, a 57-year-old man was operated upon under similar conditions. Six days after subtotal resection, there was leakage from the duodenal stump requiring drainage, this patient did well following his second operation.

As a result of these experiences, and others which we had observed on the wards of the hospital, two of us undertook a study of the records of a group of patients who had had subtotal resection of the stomach for duodenal ulcer.

At the Massachusetts General Hospital subtotal resection is the accepted operation for intractable duodenal ulcer. By subtotal resection, we mean a removal of the distal two-thirds of the stomach to or beyond the pyloric ring, or the removal of all of the distal two-thirds except a small segment of the antrum from which the mucosa has been excised.

For purposes of this study, we have excluded those patients who had emergency operations because of acute massive hemorrhage and those patients upon whom subtotal resection was performed after some previous elective surgical procedure had been carried out on the stomach.

In this paper the hospital morbidity and mortality in 175 subtotal resections done in the period 1936-1941 will be analyzed and contrasted with the results in 145 resections in 1942 and 1943. As one of many factors producing an improvement in the second group, a technic for the performance of subtotal gastrectomy in two stages will be described.

## IMMEDIATE RESULTS FOLLOWING SUBTOTAL RESECTION OF THE STOMACH MASSACHUSETTS GENERAL HOSPITAL 1936-1941

One hundred and seventy-five subtotal resections of the stomach were performed from 1936 through 1941. Fifty-five of these operations were per-

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† Now Major, M C, A U S



TABLE I  
PEPTIC ULCER  
179 PRIMARY RESECTIONS OF THE STOMACH FOR PEPTIC ULCER  
MASSACHUSETTS GENERAL HOSPITAL—1936 THROUGH 1941

Location	Operative Procedure	Cases	Deaths	Mortality Per Cent
Stomach	Classical subtotal resection	55	0	0
Duodenum	Classical subtotal resection	106	8	7.5
	Antrum left in (Finsterer)	5	1	20
	Antrum in mucosa excised	7	1	14
	Subtotal resection in two stages	6	0	0
Totals		179	10	5.6
Duodenal ulcer totals		124	10	8.1

formed for gastric ulcer, with no death. One hundred and twenty-four operations were undertaken for duodenal ulcer, with ten deaths, a mortality of 8.1 per cent. The various types of operations are shown in Tables I-IV.

Not only the fatal but also the nonfatal complications have at times proven to be very trying in this group of patients, and the 124 cases of duodenal ulcer were carefully studied from this point of view. The results of this study are grouped in Table II. There were 27 major postoperative

TABLE II  
DUODENAL ULCER  
COMPLICATIONS FOLLOWING 124 SUBTOTAL RESECTION OF THE STOMACH  
MASSACHUSETTS GENERAL HOSPITAL—1936 THROUGH 1941

	Fatal	Nonfatal
Peritonitis		
Cause undetermined	2	0
Duodenal stump	3	4
Pulmonary	2	6
Hemorrhage (K deficiency)	1	0
Malfunction of stoma	0	17
Miscellaneous	2	0
Total complications—Fatal and nonfatal	10	27=37 or 30%

TABLE III  
CAUSES OF DEATH IN 10 FATAL CASES AFTER RESECTION OF THE STOMACH FOR DUODENAL ULCER  
MASSACHUSETTS GENERAL HOSPITAL—1936 THROUGH 1941

Case No	Age	Anesthesia	Type of Operation	Cause of Death	Comment
31312	51	G O E	Finsterer with antrum left in	Peritonitis * cause undetermined	Stomach freed to pylorus 'stump turned in with difficulty
112986	62	G O E	Classical resection	Peritonitis from duodenal stump. No leak demonstrated*	Recent hemorrhage active ulcer
118122	33	G O E	Antrum in mucosa excised	Bronchopneumonia, ? peritonitis	"Large mass at ulcer site"
285787	44	Spinal	Classical resection	Peritonitis—rupture of stump*	'Stump never properly turned in
158555	51	G O E	Classical resection	Peritonitis—rupture of stump*	Ulcer broken into
201442	45	Local—Procaine	Classical resection	Hemorrhage—K deficiency	
306645	68	G O E	Classical resection	Bronchopneumonia	Recent hemorrhage
295426	50	G O E	Classical resection	Bronchopneumonia General peritonitis*	Difficulty with anesthesia
98256	49	G O E	Classical resection	Coronary thrombosis*	Nearly ready for discharge
290661	54	G O F	Classical resection	? Uremia	

\* Autopsy

TABLE IV  
ANALYSIS OF 10 CASES OF PERITONITIS FOLLOWING RESECTION FOR DUODENAL ULCER  
MASSACHUSETTS GENERAL HOSPITAL—1936 THROUGH 1941

Case No	Age	Sex	Past and Present Complications	Type of Procedure	Postoperative			Autopsy	Cause of Peritonitis
					Technical Difficulty	Day of Discharge	Result		
112986	62	M	1 Past and recent hemorrhage 2 Past perforation 3 Obstruction	Classical resection	Induration around pylorus	8	Dead	Yes	Infection arising at duodenal stump but no gross perforation
158555	51	M	1 Past hemorrhages	Classical resection	Ulcer broken into dissecting it off the pancreas Comment that he wished he had done a resection with exclusion	51	Dead	Yes	Perforation duodenal stump evident at autopsy
31312	51	M	1 Past hemorrhage 2 Past obstruction	Finsterer, with antrum left in	Stomach freed to pylorus "Turn-in with considerable difficulty" Large mass "but all went smoothly" No manipulation of mass	6	Dead	Yes	Not evident at autopsy Probably manipulation of infected area Unknown No autopsy
118112	33	M	1 Present obstruction 2 Past perforation	Antrum in, mucosa excised	Difficulty with adhesions No trouble with stump	3	Dead	No	Unknown
295426	50	M	None	Classical resection	Difficulty with adhesions No trouble with stump	6	Dead	Yes	Unknown
285787	44	M	1 Present obstruction 2 Past perforation	Classical resection	Much trouble with duodenal stump which was broken into and never properly closed	14	Dead	Yes	Duodenal stump leak evident at autopsy
79334	44	M	1 Past perforation 2 Present mild obstruction	Classical resection	Many adhesions from old operation Very dense Duodenal stump indurated Turn - in not satisfactory	35	Living		Probably duodenal stump
219882	52	M	1 Past hemorrhage	Antrum in Mucosa excised "No dissection in region of duodenum"	Inflammatory tissue around duodenum but operator said he kept away from it	30	Living		Duodenal stump (proven by operation for drainage)
215524	57	M	1 Past hemorrhages	Classical resection	Trouble with stump Short anterior flap available for turn-in	33	Living		Leak from duodenal stump
176835	61	M	1 Past hemorrhage 2 Present obstruction	Classical resection	None	28	Living		Leak from duodenal stump

complications in this group which were not fatal, but which did endanger the life of the patient and prolonged his hospital stay. Thirty-seven, or 30 per cent of this entire group, either died or had some serious complications. In addition to this, 36, or 31 per cent of the patients surviving operation, had an elevation of temperature to 101° F, or more, which did not return to a normal level until at least six days after operation.

A study of the causes of death in the ten fatal cases is instructive (Table III). Five, or one-half of the deaths, resulted from peritonitis, proven at autopsy, and a sixth case had clinical findings consistent with peritonitis. In three of these cases, the autopsy findings definitely showed the duodenal stump to be the source of the peritonitis. In two of the cases, it was impossible to determine where the peritonitis had originated. Pulmonary complications accounted for only two deaths.

Because our own experience has strongly suggested that the duodenal stump and its management played an important rôle in the morbidity and mortality following subtotal resection for duodenal ulcer, the group of ten patients having peritonitis following resection were studied with particular care. In seven of these ten cases, the infection arose from the duodenal stump (Table IV).

COMMENTS—A review of this group of cases, some of the more important aspects of which are discussed above, gives rise to certain questions. Why is a subtotal resection for gastric ulcer so much safer than it is for duodenal ulcer? During a period at the Massachusetts General Hospital when the great majority of resections of the rectum and large bowel for cancer are performed by the Resident and Junior Visiting staff, why are 64 per cent of the resections for duodenal ulcer performed by the Senior members of the staff, with a mortality of over 8 per cent? If subtotal resection of the stomach is the proper treatment for those cases of ulcer requiring surgical intervention, should it not be brought into the group of operations which can be safely and well done by any good abdominal surgeon who understands the basic principles of intestinal resection and anastomosis?

Duodenal ulcer is a disease of young and middle-aged people. The average age for this entire series is a little over 48 years, the youngest being 17 and the oldest 76. If the patient survives operation, he has an excellent chance of being cured and living a useful and productive life. It seemed proper, therefore, that certain objectives should be laid down for the management of these cases in a large general hospital such as ours. These were formulated somewhat as follows. The mortality for a resection for duodenal ulcer should not exceed that following the same operation for gastric ulcer. Since duodenal ulcer is a benign lesion, since the average age of our patients is 48 years, and since most patients who come to a resection for duodenal ulcer have been invalided for varying periods of time, expenditure of time becomes secondary to a successful and safe operation.

According to our concept of a subtotal resection of the stomach for

duodenal ulcer, the procedure really amounts to two distinct operations. First, the freeing of the duodenum and a satisfactory inversion of the duodenal stump. In the presence of an active ulceration with or without surrounding induration and edema, this may be a very formidable and time-consuming procedure, it may be trying to the surgeon and dangerous to the patient.

The second phase of the operation is the removal of an adequate amount of stomach and a careful gastrojejunostomy. This is usually the easier of the two. It is also the more important to the patient surviving operation, since the permanent benefit which he derives will depend upon the removal of an adequate amount of stomach and a satisfactory gastrojejunostomy. As described and carried out by most surgeons, the anastomosis is performed after the duodenal stump has been freed and turned in. This means that in many instances there has been local soiling, the operator may have been working under tension and be tired, and many times the anastomosis is not carried out with the care and deliberation which is essential to the best results. It is on the basis of this reasoning that in selected cases we proposed to carry out subtotal gastrectomy in two stages.

#### SUBTOTAL RESECTION OF THE STOMACH IN TWO STAGES

Since the early days of subtotal gastrectomy, the problem of the duodenal turn-in has vexed the surgeon dealing with duodenal ulcer. In 1918, Finsterer,<sup>1</sup> who at that time had already had a wide experience with gastrectomy in various forms and had performed 200 anastomotic procedures involving removal of the stomach, described his "resection for exclusion" (of the ulcer). In this paper he refers merely to the procedure of transecting and doing a turn-in proximal to the ulcer, stressing that massive gastric removal and not excision of the ulcer itself is the *desideratum* of the operation. He states that in five out of 24 cases he had left the ulcer in, with no untoward results.

He then goes on to say that if the ulcer is near the pylorus and the surgeon elects a resection for exclusion, this naturally involves transecting the stomach proximal to the pylorus, in which case the antral mucosa should be excised. He does not give any details of how he does this. He quotes Edkins'<sup>2</sup> work of 12 years before, showing the importance of antral tissue in the hormonal control of gastric secretion.

Wilmanns,<sup>3</sup> in 1926, states that for two and one-half years he had been trying Doctor Finsterer's procedure of excluding the ulcer, and that whenever this involved transection proximal to the pylorus he carefully excised the mucosa and closed the seromuscular remnant with a "button-stitch." Of 37 cases using this technic, he had had one postoperative death. He does not state how many of these actually involved antral mucosa excision, as the transection was proximal to the pylorus only in those cases where this was rendered technically essential by the inflammatory process around the pylorus.

In 1931, Druner<sup>4</sup> reiterated this thought, simply stating that antral mucosal

removal is mandatory if the duodenal pathology precludes transection distal to the pylorus. Bancroft,<sup>5</sup> in 1932, described this maneuver and brought it to light in the English literature. Since that time, this procedure has been tried in several clinics, frequently with attendant technical difficulties. Wangensteen<sup>6</sup> reports two subphrenic abscesses in 13 operations, and recommends approximation of the muscular surfaces of antral wall rather than the usual type of turn-in. Allen and Welch<sup>7</sup> had one death in their first 13 cases of mucosal excision, but have subsequently followed Wangensteen's recommendations with satisfaction. Excision of the antral mucosa involves a bloody dissection with the stomach open and, therefore, potentially contaminates the field with virulent organisms, it involves the closure of a denuded and bleeding seromuscular pocket which has often been found to be difficult.

The resection for exclusion, as conceived by Finsterer, seemed to us to represent the ideal first step of a two-stage procedure having as its objective the safe removal of the entire lower two-thirds of the stomach. It was anticipated that after six to twelve weeks had elapsed, the inflammatory process around the duodenum would subside, the ulcer probably heal, and excision of the antral segment could then be safely, if not too easily, undertaken.

Stimulated by this background and by the statistical incidence of post-operative complications traceable to technical difficulties centering about the removal of posterior wall duodenal ulcers in the acute phase, the occurrence of an opportunity to try the new technic was welcomed. Early in 1941, a patient with a bleeding duodenal ulcer was seen in consultation at the Palmer Memorial Hospital. He presented an extremely difficult problem. Fifty-two years of age, with an eight months' history of ulcer, he had been bleeding for two days and was in a severe state of nutritional depletion and acute blood loss. Attempts to transfuse him into acceptable shape for surgery produced extreme thermal reactions which, in retrospect, were probably due to anti-Rh agglutinins in his serum. Furthermore, a complete pyloric obstruction aggravated his physiologic imbalance. We did not then, and do not now, think that gastro-enterostomy is a satisfactory operation for this, or for any patient with an active ulcer. Therefore, an operative procedure permitting the ulcer to heal or removing it seemed the only solution to the problem, yet the patient, with an active posterior wall ulcer, a protein of 5.3 per cent, and commensurate disorder of water and electrolyte balance, fell into the group of patients with duodenal ulcer who are the poorest risks.

Through a left paramedian incision the stomach was transected at the angulus and dissection carried towards the fundus, transecting the stomach at the level of an adequate subtotal resection and the anastomosis done. Attention was then turned to the antral end of the stomach, the duodenum was seen to be involved in an extensive acute inflammatory mass. Therefore, the antral end of the stomach was turned in and the abdomen closed. The patient's convalescence was uneventful, he had no further bleeding, and six weeks later the antral end of his stomach was removed through a right

muscle-splitting incision. At this operation the field of anastomosis and previous dissection was not entered or disturbed in any way. The duodenal mass had disappeared, and the tissues in that region, while scarred and adherent, had lost their inflammatory character, were no longer involved in an acute process, and their removal was a relatively simple matter.

In this way the patient had been given an adequate subtotal gastrectomy conforming in every way to present day concepts, yet with a minimum of risk and operative trauma and without excessive expenditure of time.

Since that time, this procedure has been found useful in situations where removal of duodenum in the acute phase of ulceration rendered subtotal gastrectomy unjustifiedly hazardous.

This procedure has now been carried out in 37 cases, and our experience with it is extensive enough to draw conclusions as to its place in gastric surgery.

We are of the opinion that the two-stage gastrectomy will find usefulness for the skilled and experienced gastric surgeon in the occasional case where the inflammatory fixation of pylorus and duodenum destroys landmarks and renders adequate duodenal closure difficult or impossible. For the surgeon whose practice includes only occasional gastric resections, the two-stage operation offers a safe and reliable procedure which will not subject his patient to an unreasonably long or shocking operation. For the Resident who is beginning his gastric experience and who wishes to take adequate time and care for each maneuver involved in a resection, the procedure is ideal. At first, he can do the second stage, becoming acquainted with duodenal turn-in procedures, then going to first-stage operations, learning to perform a careful anastomosis in an unhurried fashion. Finally, he is ready to perform the one-stage operation at a time when he has gained self-confidence and practice in both phases of the procedure.

#### OPERATIVE TECHNIC

As a result of our study of the group of cases mentioned above, and of our experience with the two-stage operation, we have formulated a definite plan in teaching the Resident Staff on our Service the technic of subtotal resection for duodenal ulcer. This plan utilizes the knowledge that the removal of the proximal segment of stomach is most easily accomplished with the distal end divided and free to manipulate, whereas, the dissection around the pylorus is most readily accomplished when approached from the left, with the stomach free. It emphasizes the importance of careful removal of an adequate amount of stomach and a careful, unhurried anastomosis. The details of technic are shown in the accompanying illustrations.

A Levine tube (Nos. 18 or 20 F) is passed into the stomach on the morning of operation and is kept on gentle suction throughout the operation.

*First Stage*—The abdomen is opened through either a left subcostal or a left paramedian incision. The stomach is transected between clamps at a point at least eight centimeters proximal to the pylorus. If the stomach

is large and markedly edematous, the point of transection should be still higher. It is of extreme importance in selecting the point of transection that a sufficiently long segment of stomach be left at the pylorus to facilitate the antral turn-in if this should be indicated. This will usually take more stomach than at first seems necessary. The antium is roughly a triangle with the apex at the pylorus, if the segment is too short, it becomes difficult or impossible to turn the wide base into the relatively narrow apex.

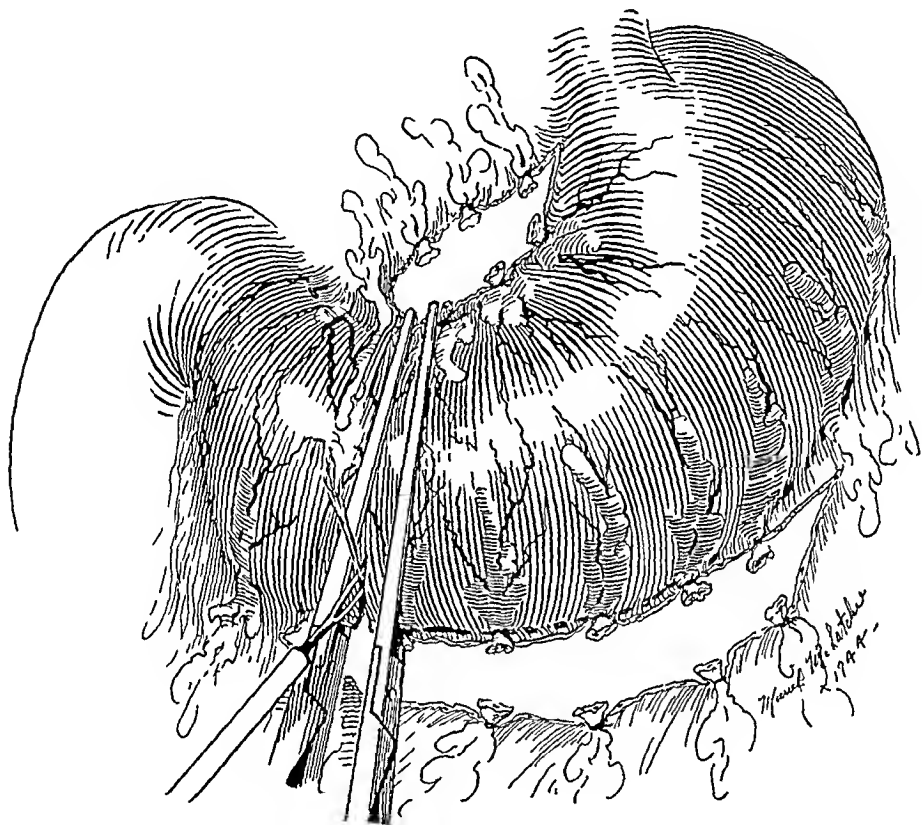


FIG. 1.—The stomach is transected with a cautery between clamps at least 8 cm proximal to the pylorus.

Each cut end of the stomach is covered with a gauze sponge which is tied in place. A subtotal resection on the proximal segment is carried out at the point of election, a gastrojejunostomy is then performed. We prefer a posterior anastomosis of the Hoffmeister-type, and if, for any reason, this is difficult or impractical, an anterior anastomosis, using a long segment of the jejunum (approximately 30 cm from the ligament of Treitz), is established.

We believe that this procedure should be carried out with deliberation and care and every effort made to minimize trauma, and contamination. We are particularly careful to avoid manipulation of the jejunum and under surface of the transverse mesocolon, which will later come in contact with the region of the anastomosis. We believe that local soiling, trauma, and resulting adhesions play an important part in postoperative stomal obstructions.

## GASTRECTOMY FOR DUODENAL ULCER

While many surgeons prefer the use of nonabsorbable sutures, and feel that they are essential to satisfactory results, we use continuous Nos 00 or 000 chromic catgut for both the outside and inside layers. If a fine suture is used, we feel that the care and precision with which the anastomosis is made is of greater importance than the type of material used. If a posterior anastomosis is used, great care is taken to suture the transverse mesocolon at least one centimeter, preferably two centimeters above the line of anastomosis.

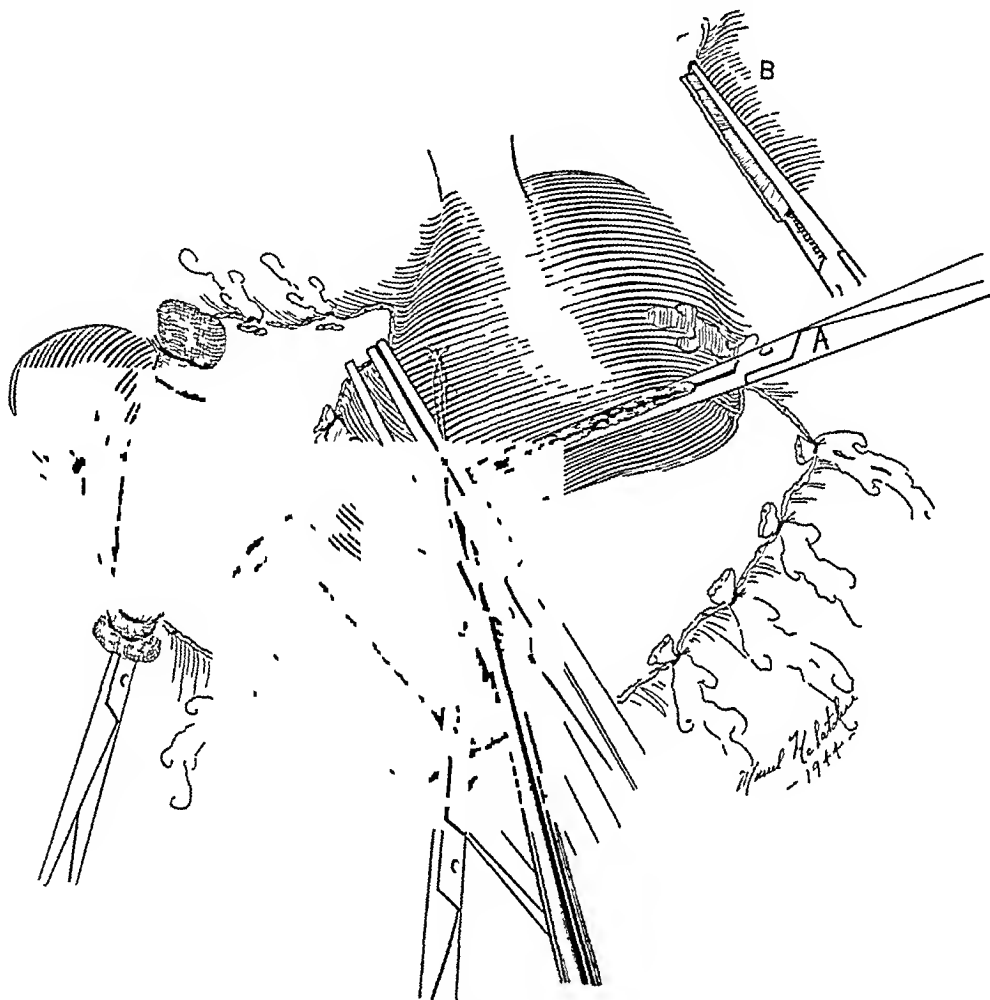


FIG 2—Each cut end is covered with a gauze sponge, a subtotal removal of the proximal segment is carried out. The gastric remnant is prepared for a Hofmeister anastomosis. The clamp (A) applied from the greater curvature side is at right angles to the long axis of the stomach and should not be angulated towards the esophagus. The triple clamp technic is used on the lesser curvature side to facilitate inversion. Insert (B) shows the crushed end after removal of the outside clamp, this is closed with an over and over suture before the second clamp is removed.

After the completion of the anastomosis, attention is turned to the antral stump. If there is an inflammatory reaction present, if the duodenum is edematous or adherent, or if there is any question in the judgment of the operator as to the advisability of completing the operation in one stage, the end is closed with a double layer of catgut and a single layer of fine cotton or silk, and the operation concluded. If, however, the patient is in good condition, and the duodenal stump is flexible, the operation is completed in one stage.

Early in our experience with this operation, we were apprehensive about the safety of closing the antral segment in a patient with a high degree of



obstruction We have now done this in patients who were clinically completely obstructed, and it is our conviction that if an adequate remnant of antrum is left, so that the end can be turned in without trauma or tension, there

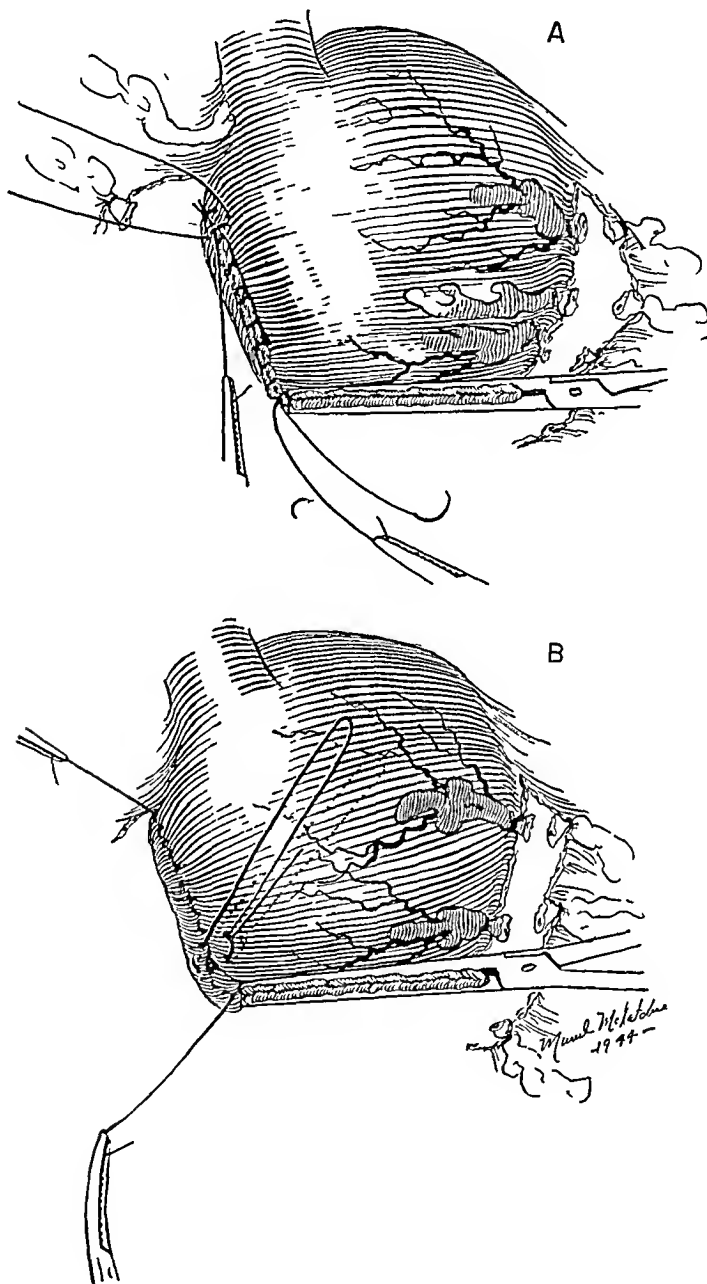


FIG 3—Preparation of the gastric remnant for the anastomosis. The crushed end has been sutured and the clamp removed. By gentle downward traction on the end of the first suture (A) the upper end is easily and completely inverted. Triple zero catgut is used for these layers, a third layer of interrupted No 70 cotton or No 3 silk is used as the outside layer.

will always be opening enough through the narrowed duodenum to permit passage of the very small amount of secretion which will be present from the antral mucosa.

Jejunostomy for feeding purposes is performed upon patients with diabetes

mellitus and in those patients whose nutritional status is exceptionally poor and where immediate jejunal feedings are indicated

*Second Stage*—Depending upon the condition of the duodenum at the time of the first stage, the second step is carried out in from three to twelve weeks after the initial operation. The patient is usually discharged in 14 to 16 days after the primary operation. If too short an interval between operations is chosen, the removal of the antral stump and a satisfactory duodenal turn-in will be unnecessarily difficult. If the interval is too long, there is the definite hazard of the development of a jejunal ulcer.

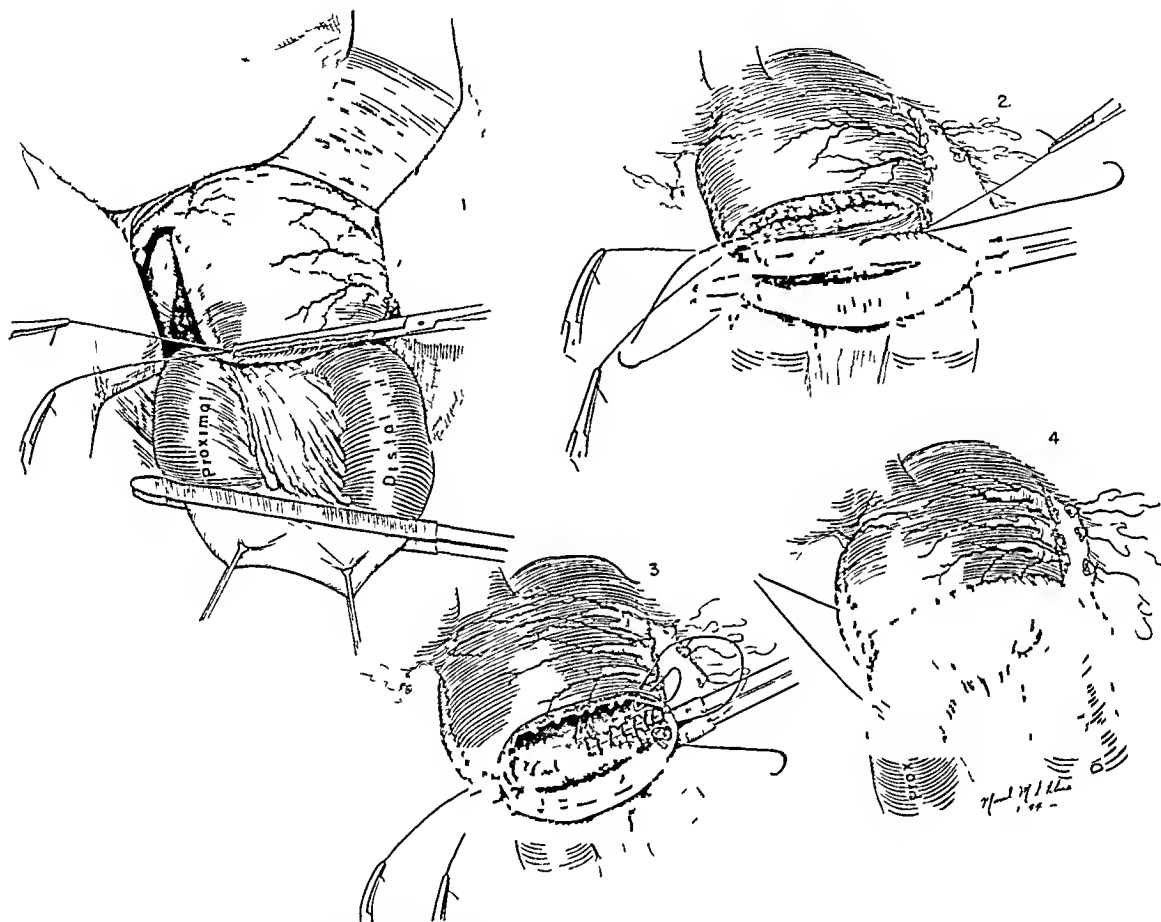


FIG. 4.—The anastomosis is carried out as shown above. The distal loop of the jejunum is placed at the greater curvature end of the stomach. A rubber covered clamp is placed on the jejunum but not on the stomach. Two layers of No. 00 or No. 000 catgut are used, the anterior layer and ends are reinforced by a few No. 70 cotton sutures. The proximal loop about 1 cm. below the line of anastomosis is sutured to the lesser curvature of the stomach to protect the inner corner and to relieve any tension from the end of anastomosis.

The abdomen is opened through a right-sided incision, a subcostal incision being an excellent approach. We have also used a right rectus-splitting and a paramedian incision. The antral segment is readily found, the adhesions at its proximal end are freed without difficulty, and the dissection carried down to a level at which a satisfactory duodenal turn-in can be obtained. It is not necessary to remove the ulcer site. If it is immediately distal to the pylorus, the dissection will usually be carried past its bed and an easy turn-in obtained. There can be no standard method for turning in this duodenal stump. It may be done in one of the classical methods as shown in the accompanying

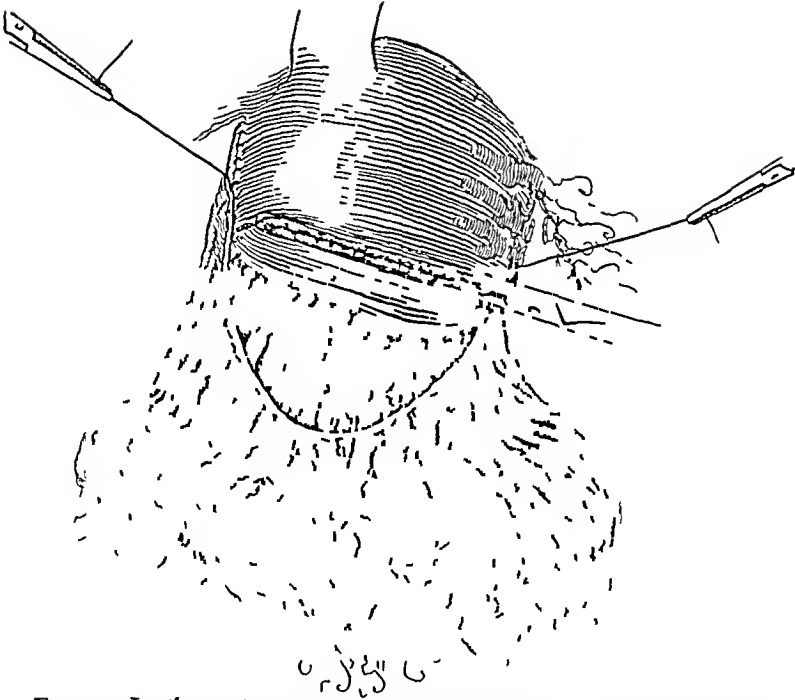


FIG 5—In the posterior gastrojejunostomy the cut edge of transverse mesocolon is sutured to the posterior surface of the stomach before the anastomosis is started. This suture line is at least 2 cm. above the line of anastomosis. Great care is taken to avoid trauma in the region of the anastomosis, particularly to the under surface of the mesocolon. All possible manipulation is done from above.

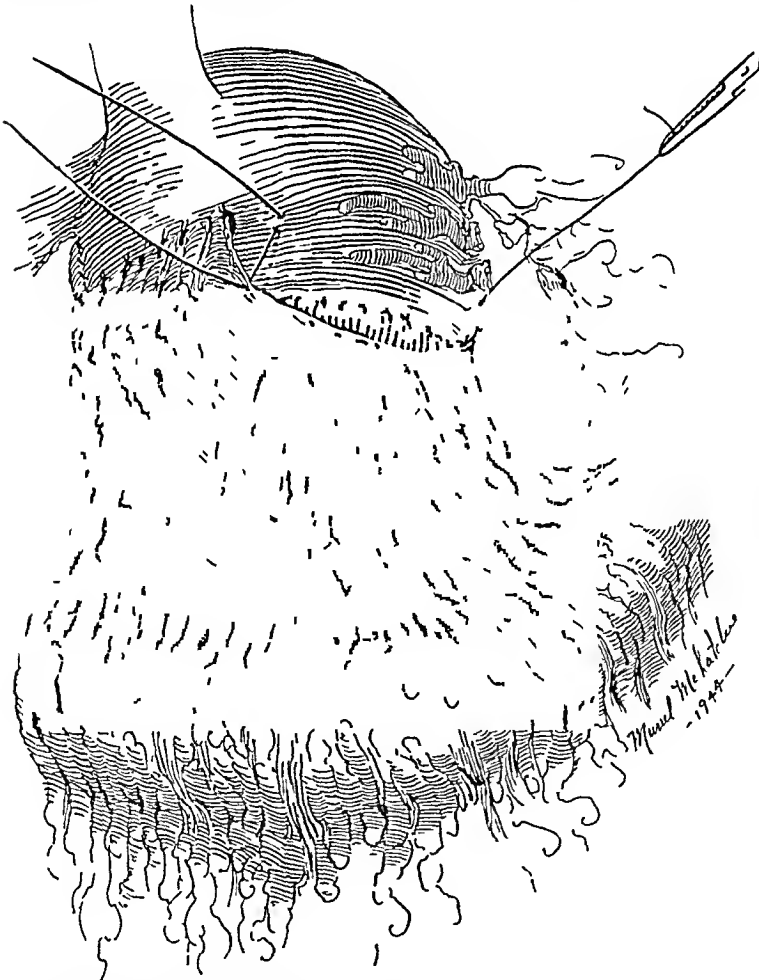


FIG 6—Posterior Hofmeister anastomosis. Suture of transverse mesocolon well above line of anastomosis at completion of gastrojejunostomy. We are now using a continuous No. 70 cotton for this suture.

illustration At times the lumen is extremely small so that a tie may be applied and the end turned in, not unlike an appendix stump Our experience with one difficult case, in which the common and pancreatic ducts were both divided during the course of an extremely careful dissection, convinces us that there is the occasional case in which the ulceration has been so large that when the contracture of healing has taken place, it will be unsafe and unwise to attempt dissection down onto the duodenum Although we have not yet

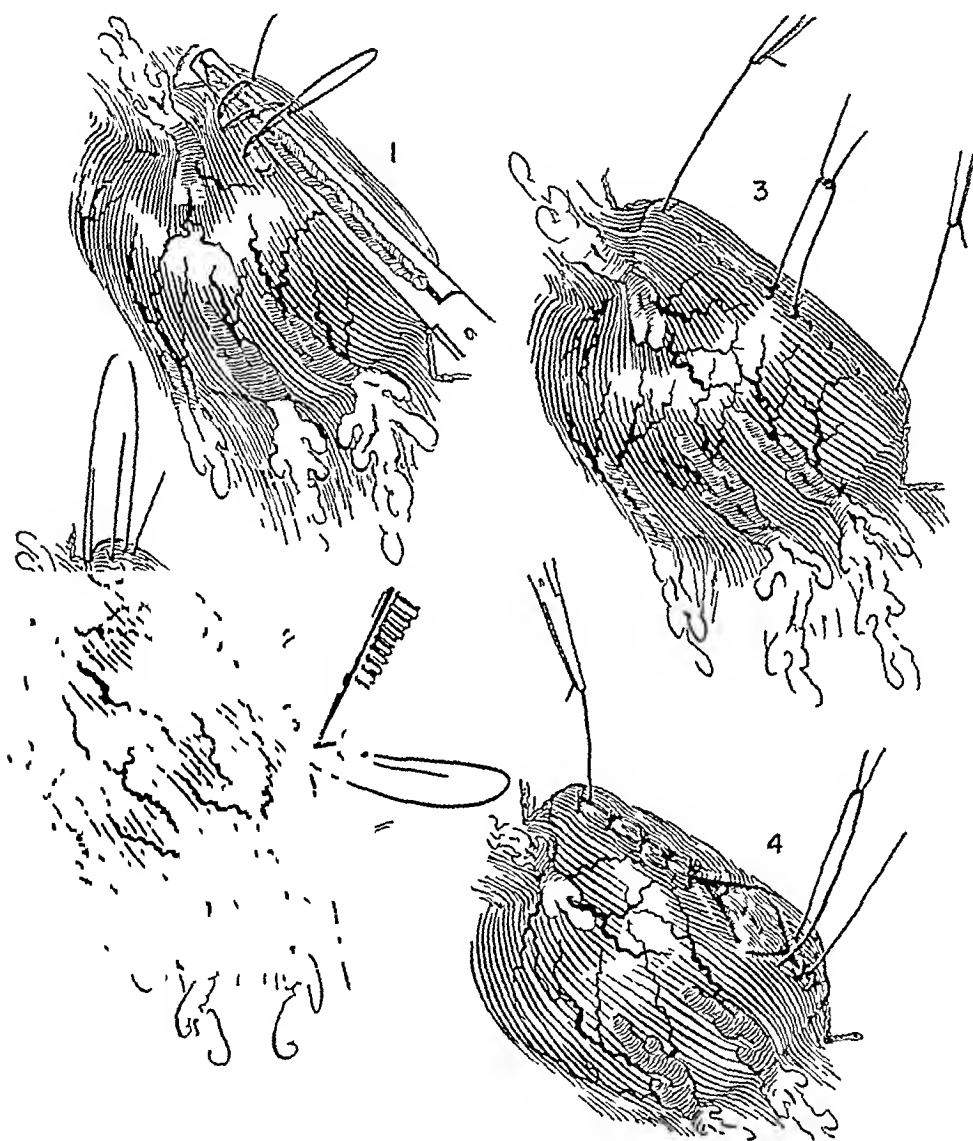


FIG 7—Steps in closure of antral stump as final step in first stage of two-stage operation Two layers of continuous No 00 catgut are used and a third layer of interrupted No 70 cotton Note that in second and third layers the inversion always starts from each corner and ends in the middle

done it, we feel quite convinced that there will be the occasional case in which the removal of a portion of the antrum and excision of the remaining antral mucosa will be the procedure of choice If this procedure is elected, we strongly advocate the technic as described by Wangenstein in which no attempt is made to invert the antral end, but rather to approximate carefully the denuded muscular surfaces

## RESULTS IN TWO-STAGE GASTRECTOMY

Forty-three patients have had two-stage gastrectomies performed at the Massachusetts General Hospital and Baker Memorial, or in private practice at the Palmer Memorial Hospital and Phillips House. Of these, four do not fall into the primary series comparable to the one-stage gastrectomies reviewed in the foregoing sections because they either had previous corrective gastric surgery or were operated upon as an emergency procedure because of massive bleeding.<sup>1</sup> One patient had an atypical two-stage procedure not conforming to the technic herein described.

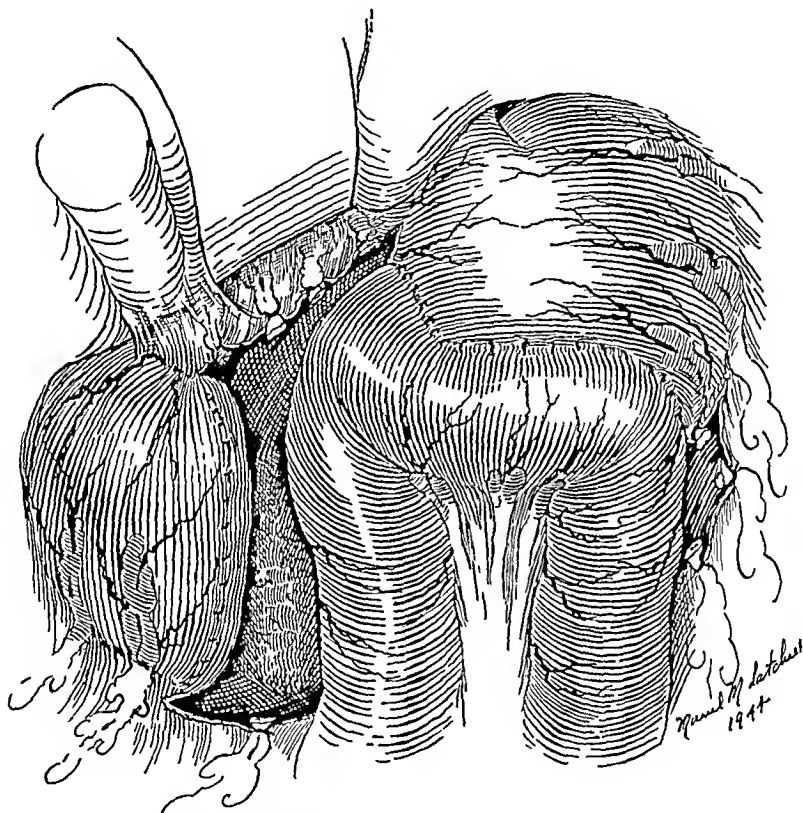


FIG. 8.—Completed first stage operation (anterior Hofmeister gastrectomy). Note that there has been no dissection of the antral segment.

The remaining 39 cases, however, are pertinent to these statistics, have had the two stages completed and have been followed long enough to be subject to analysis. There have been no deaths.

These 39 patients are distributed as follows in regard to their service:

M G H	28
West Surgical Service	22
East Surgical Service	6
Private cases	11

\*The two-stage operation is not indicated for acute massive hemorrhage. It was done in this one case because the local condition of the duodenum forbade any type of direct attack on the ulcer. He died one week later. No autopsy could be obtained, but no subsequent bleeding had occurred.

## GASTRECTOMY FOR DUODENAL ULCER

The age distribution is essentially that of duodenal ulcer in general, as shown in Table V. It is of interest that two of the patients were in their 'teens, and two in the eighth decade of life

TABLE V  
TWO-STAGE GASTRECTOMY  
AGE DISTRIBUTION

Age-group	No of Cases	Per Cent
10-20	2	5 1
21-30	0	0
31-40	7	18 0
41-50	7	18 0
51-60	13	33 3
61-70	8	20 4
71-80	2	5 2
	<hr/> 39	<hr/> 100 0

Of the 39 patients in the group, 36 are males, 3 females. Seventy per cent had their operative program completed prior to July, 1943, and have been followed for a year or more

TABLE VI  
TWO-STAGE GASTRECTOMY  
INDICATIONS FOR GASTRECTOMY

	No of Cases	Per Cent
Intractability	5	12 8
Obstruction	16	41 0
Obstruction + recent perf	3	7 7
Obstruction + bleeding (past)	6	15 4
Total obstructed	25	64 1
Recent severe hemorrhage	6	15 4
Carcinoma of pylorus?	3	7 7
	<hr/> 39	<hr/> 100 0

The indications which brought these patients to surgery are shown in Table VI. It should be noted that 65 per cent of the group had obstruction in one form or another and that almost 80 per cent were either obstructed, had bled, or both. This emphasizes the fact that the two-stage gastrectomy finds its greatest usefulness in the extremely poor-risk patient.

The reasons for selecting a two-stage procedure are tabulated in Table VII. It is significant that 80 per cent of the patients had a two-stage procedure.

TABLE VII  
TWO-STAGE GASTRECTOMY  
INDICATIONS FOR TWO-STAGE GASTRECTOMY

	No of Cases	Per Cent
Local duodenal and pyloric reaction	20	51 3
Local reaction + poor risk	5	12 9
Local reaction + recent hemorrhage	1	2 6
Local reaction + obstruction	5	12 9
Total local reaction, etc	31	79
Obstruction + poor risk	4	10 0
Obstruction + bleeding	1	2 6
Peculiar build & mechanics of oper	1	2 6
Recent hemorrhage + poor risk	2	5 1
	<hr/> 39	<hr/> 100 0

selected because of locally difficult conditions at the duodenum. This is the indication *par excellence* for delaying antral removal and allowing the inflammatory process to subside.

We have stressed in the previous section that the two-stage procedure is well adapted to training of residents. In Table VIII is shown the status of

TABLE VIII  
TWO STAGE GASTRECTOMY  
STATUS OF OPERATING SURGEONS  
MASSACHUSETTS GENERAL HOSPITAL

First Stage	No of Cases	Per Cent
Senior Visiting Surgeon	13	46.4
Junior Visiting Surgeon	9	32.2
Resident Surgeon	6	21.4
	28	100.0
Second Stage		
Senior Visiting Surgeon	2	7.4
Junior Visiting Surgeon	5	18.5
Resident Surgeon	20	74.1
	27	100.0
Total operations by Residents	26	47.8

TABLE IX  
TWO-STAGE GASTRECTOMY  
COMPLICATIONS OF THE FIRST-STAGE OPERATION

	No of Cases	Per Cent
No complications	34	87
Complicated	5	13
Malfunction requiring jejunostomy (jejunostomy 16th day—stoma opened 32nd day)	1	
Fever and jaundice (cleared spontaneously without explanation)	1	
Pulmonary edema requiring oxygen (?fluid—?bronchitis)	1	
Unexplained temp rise to 102° F (no explanation)	1	
Hepatitis—jaundice—?pulm infarct (probably sulfonamide toxicity)	1	
No deaths		
One jejunal ulcer at 3 months healed excision of antrum (2nd stage)		

surgeons performing the two operations on the Massachusetts General Hospital cases. It is noteworthy that over 20 per cent of the first-stage operations and 75 per cent of the second-stage operations were performed by the Resident Staff. It should be recalled in this connection that this group of patients falls into the bad-risk group, and yet, by employing the two-stage maneuver, fully 50 per cent of the total number of operations may be performed by the Resident Staff with safety.

#### COMPLICATIONS OF THE TWO-STAGE PROCEDURE

In Table IX are shown the complications of the first-stage operation. One, a malfunctioning stoma, was a major complication and required a jejunostomy. The stoma opened on the 32nd day, and the patient has done well since. This patient had coexistent polycythemia vera. The other four complications

were minor and evidently unrelated to the technical procedure employed. All subsided spontaneously.

In Table X are shown the second-stage complications. Three of the 37 second-stage operations developed complicated courses. Two of these were unrelated to the technical procedure and subsided without treatment.

TABLE X

TWO-STAGE GASTRECTOMY

COMPLICATIONS OF THE SECOND-STAGE OPERATION

	No. of Cases	Per Cent
No complications	36	92.3
Complicated	3	7.7
Pulmonary edema requiring bronchoscopy	1	
Hepatitis, pulm. infarct?	1	
Stump blowout, with subdiaphragm abscess	1	
No deaths		

The patient with hepatitis and a pulmonary infarct had had the same combination following his first operation, the same is true of the pulmonary edema developed by one patient. The latter case would have done better had he had his second stage done under local or spinal anesthesia rather than gas-oxygen-ether which, apparently, produced considerable bronchitis and edema.

One of the second stage complications was major and almost cost the patient his life. This was a very difficult duodenal turn-in in an adherent posterior wall ulcer. The patient developed a periduodenal abscess which was drained and a duodenal fistula which closed spontaneously. He then developed a left subphrenic abscess which was drained, this healed, and he has done well since. One cannot but speculate on what havoc would have been wrought by this sepsis in a patient with a fresh gastrectomy. However, in this patient the resection and anastomosis had been done seven weeks before, and through his stormy second-stage convalescence he never developed any evidence of nutritional imbalance or stomal malfunction.

Another patient whose postoperative course was quite smooth and who does not, therefore, fall into the group of postoperative complications, nevertheless, had intraoperative complications in his second-stage operation which are of considerable interest. This patient went 14 weeks between stages, and at his second stage presented an extremely adherent posterior wall ulcer, with the duodenum fused to the pancreas. In freeing up the duodenum the common and pancreatic ducts were severed. The common duct was anastomosed to the duodenum over a vitallium tube and the cut end of pancreatic duct was turned into the duodenum. The patient had a smooth convalescence, and has remained well (one year).

These last two patients have made it clear that the second stage can be complicated at times even if the inflammatory lesion has subsided and adherent scar is the only residual. We have found that difficulties are minimal.



in those cases which are allowed longest between stages. However, any wait of over three months probably begins to run the risk of jejunal ulceration. Therefore, we prefer to wait six to twelve weeks between stages and see no reason why the patient cannot return to full activity for a part of this interval.

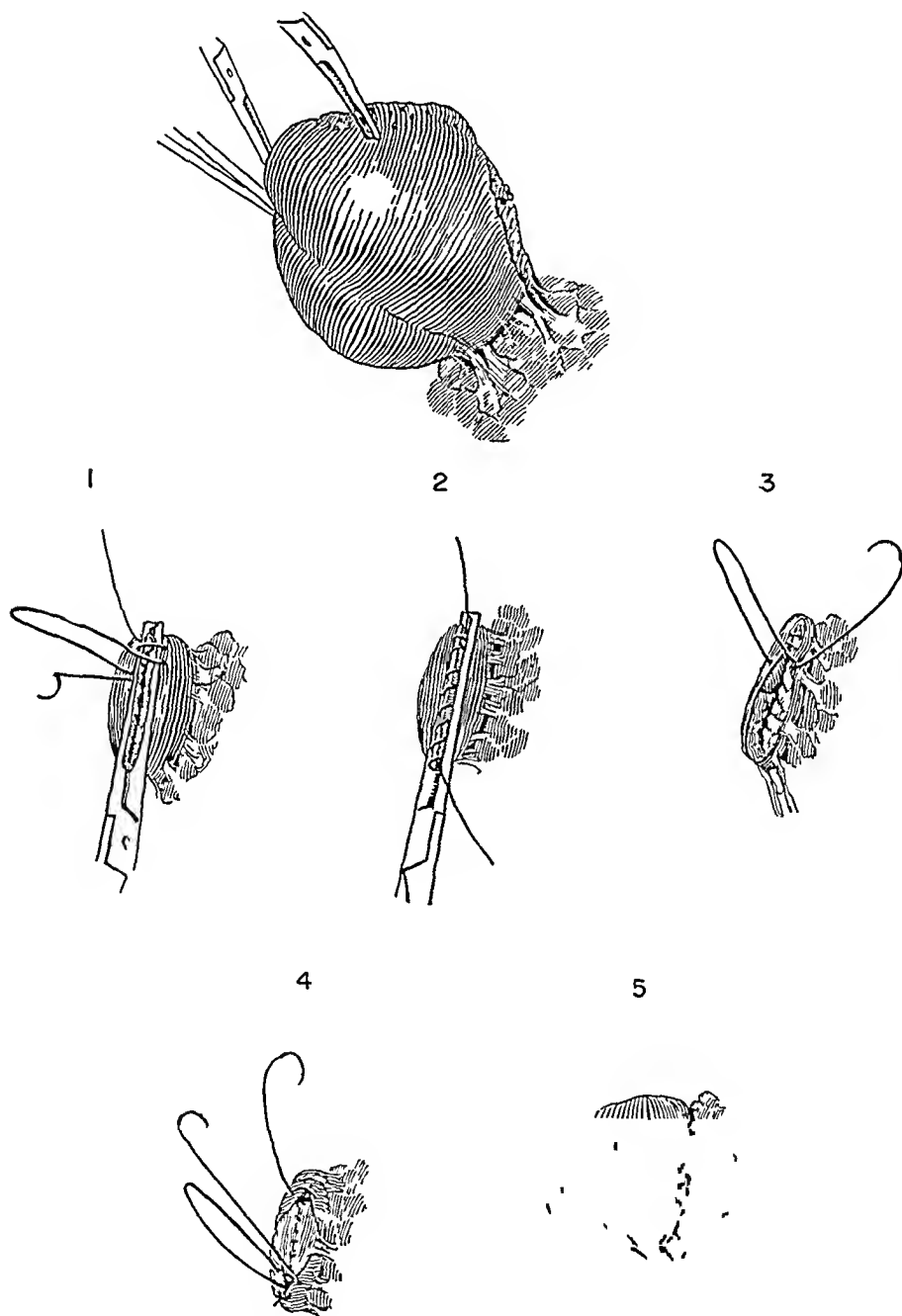


FIG. 9.—Second stage—removal of antral stump. The antrum is exposed through right upper quadrant incision. The antral stump readily identified, grasped with Allis forceps and dissected free. Inserts 1, 2, and 3 show different methods of placing first layer of sutures—depending upon length of duodenal stump. A second layer of No. 000 catgut and a third layer of interrupted No. 70 cotton are used.

RELATION OF ANTRUM TO JEJUNAL ULCER

One may ask, must the antrum always be removed? Our answer to this question is an unqualified "yes!" This conclusion is based upon three considerations

(1) Edkin's<sup>2</sup> work demonstrating that a substance in antral mucosa, injected intravenously in dogs, produces a massive gastric secretion even in isolated gastric tissue

(2) The fact that nine patients known to us, one of them in this series, developed jejunal ulcers when the antrum was left in for from three to thirty-six months after a Finsterer-type procedure

(3) The fact that all of these cases have had their jejunal ulcer cured by antral excision alone or in combination with a higher resection

Review of Edkin's work and subsequent physiologic investigation of the hormonal factors in gastric secretion cannot be detailed here. Suffice it to say that, as early as 1906, he had shown that "extracts made of the pyloric mucus membrane in boiling water or 4 per cent hydrochloric acid contain an active substance which on injection into the blood vessels of an animal leads to a secretion of gastric juice" He goes on to state that "extracts of fundus do not contain this substance"

This work suggests strongly that the antral mucosa is, in truth, an endocrine gland occupying a key position in the secretory mechanism, and that responses from its mucosa govern much of gastric secretory activity, the autonomic and intrinsic nerves governing the rest

Therefore, to encounter even one case of subtotal gastrectomy where a small amount of retained antral tissue was associated with a jejunal ulcer, and where removal of the antrum alone accomplished a cure of the ulcer, would be highly significant. We have had, now, four such cases in this hospital, as well as three others whose jejunal ulcer was only cured by re-resection where that operation included antral removal (Table XI). These leave little room for doubt concerning the necessity for removal of the antrum

The first case to be relieved of jejunal ulcer solely by antral excision was a patient who, after three gastric operations, including a subtotal resection elsewhere, entered the Massachusetts General Hospital with a large marginal ulcer (Table XI). Pain, which was severe, was unimproved by a careful medical regimen, and roentgenograms showed no change in the size of the ulcer. Realizing the potentialities in regard to antral tissue remnants, this patient was explored, and a retained antrum found. Its removal was easily accomplished and nothing further was done. Awakening from the anesthetic, the patient stated that he was free of pain. The pain did not return, and a roentgenologic examination 14 days later showed no evidence of ulcer remaining. He was still symptom-free three and one-half years later.

The second case in this group was one of the patients in our series of two-stage operations. He was a man, age 76, and had done so well following his first-stage procedure that his attending physician was somewhat opposed to running any further, possibly unnecessary, risks. He, therefore, did not

TABLE XI  
JEJUNAL ULCERS CURED BY ANTRAL EXCISION\*

	Previous Operations	Interim Findings	Admission Findings	Operation	Result
Case 1 (Male) No 234657 Age 36 Ulc hist 19 yrs	'22—PGE & ' suture of ulcer 38—PGE undone '39—(Jan ) ' Three inches of stomach removed 39—(Oct ) "Two- thirds of stomach removed (All above operations done at outside hospital)	'23—Hemorrhage '38—Jejunal ulcer '39—Hemorrhage 40—Recurrent hemorrhage '40—Feb pt entered MGH	1 5 cm marginal ulcer (x-ray) (2-26-40)	Removal of antrum (3-21-40)	Ulcer gone in 3 wks Well since (3 yrs )
Case 2 (Male) No 380013 Age 76 Ulc hist 4 mos	42—(Nov ) 1st stage gastrectomy Antrum left in for later removal (MGH)	43—(Feb ) Recur- rence of pain	Jejunal ulcer (X-ray) (9 5 43) Much pain	Removal of antrum (9 8 43)	Pain immediately relieved Ulcer much decreased in size (x-ray) in 11 days Well since (8 mos )
Case 3 (Male) No 368692 Age 30 Ulc hist 12 yrs	36—Perforated ulcer sutured 42—(Jan ) Subtotal gastrectomy (At outside hosp )	42—(Feb ) Recur- rence of pain immediately postop '42—(April ) Two hemorrhages 42—August pt entered MGH	Jejunal ulcer (X ray) (8-4-42)	Removal of antrum Lysis of adhesions Jejunostomy (8-6-42)	Decrease in size of ulcer in 3 wks Well since (1 yr )
Case 4 (Male) No 162506 Age 68 Ulc hist 2 yrs	36—(May ) Finsterer op Antrum left in '36—(Nov ) Resection of jejunal ulcer and removal of more fundus (Done at MGH)	36—Jejunal ulcer	1 3 cm marginal ulcer	Reresection plus re- moval of antral mucosa (11-4-39)	Well since Neg- ative x-ray (12-7-39)
Case 5 (Male) No 81857 Age 34 Ulc hist 10 yrs	37—(Dec ) Finsterer op Antrum left in (Done at MGH)	39—Jejunal ulcer	Jejunal ulcer	Reresection plus re- moval of antrum (2-20-40)	Well since (3 yrs )
Case 6 (Male) No 400869 Age 52 Ulc hist 21 yrs	43—(May ) 1st-stage gastrectomy Antrum left in for later removal (MGH)	43—(Oct ) Recur- rence of pain 2nd stage not done as planned	Jejunal ulcer (X-ray) (5-11-44)	Removal of antrum (5-12-44)	Pain immediately relieved Ulcer smaller 11 days Disappeared 18 days Well since
Case 7 (Male) No 430805 Age 32 Ulc hist 5 yrs	38—Perforated ulcer 43—(May ) 'Subtotal gastric resection (Outside hospital)	43—(Dec ) Jejunal ulcer	Jejunal ulcer Virtually no stomach resected	Reresection plus re- moval of antrum (12-18-43)	Well since (5 mos )

\* Dr Samuel F Marshall of the Lahey Clinic Boston Mass has kindly informed us of two additional cases of jejunal ulcer cured by antral excision This brings the total number of cases on record up to nine

One of Doctor Marshall's patients had had two gastric resections during a four-year period with persistent jejunal ulceration Removal of the antrum alone relieved the situation completely, and the patient has been well since (10 months)

Doctor Marshall's second case was a patient who had had a resection of the stomach four years previously who had recently developed a jejunal ulcer, and whose jejunal ulcer has been completely healed by resection of the antrum

have a second stage as soon as is usually planned. However, three months postoperatively, he developed signs and symptoms of a jejunal ulcer. He faced this for seven months, and then returned for operation. Roentgenograms showed a large jejunal ulcer, and a routine second-stage was carried out, the region of the previous anastomosis was not entered. He, too, was immediately relieved of his pain and 11 days later, reexamination, roentgenologically, showed marked decrease in the size of the ulcer. At the present time, eight months later, he is enjoying perfect health.

The third patient was seen by Dr. Arthur W. Allen six and one-half months after a "gastrectomy" elsewhere. He had very early recurrence of symptoms. Three months before entrance he had two hemorrhages and, on admission, a jejunal ulcer was demonstrated roentgenographically. At operation, a five-centimeter antral segment was found and removed. There was prompt relief from symptoms. Roentgenologic examination three weeks after operation showed decrease in the size of the ulcer. He has remained well (one year). Brief mention of the details of the remaining six cases of antral removal will be found in Table XI.

Allen and Welch<sup>7</sup> also stress the importance of antral excision in showing that of nine patients surviving the Finsterer procedure, with antrum left in, five developed jejunal ulcers, two being relieved by reoperation, only when the procedure included removal of antrum or antral mucosa. Ogilvie<sup>8</sup> states that of 22 patients operated upon in such a fashion as to leave antral tissue in, nine developed symptoms of recurrence and six required reoperation removing or destroying the antral mucous membrane.

Still another patient, encountered in the two-stage series, developed, just above the cardiac orifice, severe esophageal spasm with complete obstruction. He was readmitted to the hospital two months after discharge following the first stage of his resection. At discharge, roentgenologic examination showed a normal esophagus and postoperative stomach. On readmission, he complained of pain and difficulty in swallowing. These symptoms increased, the obstruction became complete, and a jejunostomy was performed. All nourishment was given directly into the jejunum for two months, without improvement in symptoms, nor could any change be noted roentgenographically. Improvement did begin shortly following excision of the antrum, and he was discharged 27 days later, symptom-free, on a soft diet. He has remained well (17 months). This case suggests that the antrum may play a rôle in upper gastro-intestinal function which goes beyond the regulation of gastric secretion.

It should be pointed out that ten of our patients have gone ten weeks, or longer, between their two stages without getting into any trouble. One patient, who was thought to have a carcinoma of the pylorus at his first operation, went five months between stages without jejunal ulceration. It is of interest that at his second stage, the duodenal mass, which had suggested carcinoma at the first operation, had subsided so completely as to render antral removal entirely uneventful.

IMMEDIATE RESULTS FOLLOWING SUBTOTAL RESECTION OF THE STOMACH  
*Massachusetts General Hospital*  
1942-1943

Between January 1, 1942, and December 31, 1943, there were 145 subtotal resections of the stomach performed for peptic ulcer at the Massachusetts General Hospital. In this series, as in the 1936-1941 series, only elective primary operations are included. Fifty-one (Table XII) of these operations

TABLE XII

## PEPTIC ULCER

145 PRIMARY RESECTIONS OF THE STOMACH FOR PEPTIC ULCER  
MASSACHUSETTS GENERAL HOSPITAL—1942 THROUGH 1943

Location	Operative Procedure	Cases	Deaths	Mortality Per Cent
Stomach	Classical subtotal resection	51	2	3.9
Duodenum	Classical subtotal resection	63	0	0
	Antrum left—mucosa removed	8	0	0
	Subtotal resection in two stages	23	0	0
Totals		145	2	1.4%
Duodenal ulcer		94	0	0

were for ulcer of the stomach with two deaths or a mortality of 3.9 per cent. Ninety-four of the operations were for duodenal ulcer and in this series of 94 cases, there were no deaths. Sixty-three of the latter operations were classical subtotal resections in one stage. In eight other cases, the antrum was left, but the mucosa removed, and in 23 patients during this period, the two-stage resection was carried out.

A study of the nonfatal complications was also made as in the preceding series (Table XIII). In this group of 94 cases there were 13 major nonfatal

TABLE XIII

COMPLICATIONS FOLLOWING 94 SUBTOTAL RESECTION OF THE STOMACH  
MASSACHUSETTS GENERAL HOSPITAL—1942 THROUGH 1943

	Fatal	Nonfatal
Peritonitis		
Cause undetermined	0	0
Duodenal stump	0	1
Pulmonary	0	4
Malfunction of stoma	0	7
Miscellaneous	0	1
Total complications—Fatal and nonfatal	0	13 or 14%

complications, or 14 per cent of the entire group. This compares very favorably with the total of 37, or 30 per cent, in the earlier series. It is of interest that there was only one case of peritonitis in this entire group, this being the nonfatal case of leak from the duodenal stump, occurring in the second stage of a two-stage procedure.

COMMENT—We are unable to give to any one procedure the credit for the improvement which has taken place during these past two years. Patients are better cared for. A better understanding of the importance of plasma, whole blood, and the parenteral use of amino-acids and vitamins has done

much to protect them before and after operation. But of greater importance is the almost complete elimination of those complications secondary to leakage or contamination from the duodenal stump. It matters little whether this be accomplished by the delayed removal of the antral segment, as described above, or by excision of the mucous membrane from the antrum in those cases where the local reaction forbids safe dissection of the ulcer-bearing area.

The two-stage method has been more freely practiced on the West Surgical Service, especially by the younger men, whereas, on the East Surgical Service, under Dr. Arthur W. Allen, equally satisfactory results have been attained in one stage by removing the antral mucosa in those cases where the local reaction was not so great as to make even this unsafe.

It is of further interest that the management of these cases after operation varies considerably on the two Services. On the East Service, under Doctor Allen, jejunostomy plays an important rôle in the postoperative regimen. Allen and Donaldson<sup>9</sup> now favor a double jejunostomy—one catheter passing upwards through the anastomosis into the stomach, for purposes of drainage, the other passing down the jejunum, for feeding.

In contrast to this, on the West Surgical Service, under the senior author, jejunostomy is undertaken only in patients with diabetes mellitus and in those patients whose nutritional states makes early jejunal feedings highly desirable.

#### SUMMARY

(1) From 1936 through 1943, 320 primary elective subtotal resections of the stomach have been performed for peptic ulcer at the Massachusetts General Hospital. There were 12 deaths, a mortality of 3.7 per cent.

(2) From 1936 through 1941, there were 55 resections for gastric ulcer with no deaths, and 124 resections for duodenal ulcer, with a mortality of 8.1 per cent.

(3) A study of the records of these patients showed contamination from the duodenal stump to have been the major factor in the high mortality.

(4) In 1942 and 1943, 51 patients had subtotal resection for gastric ulcer, with a mortality of 3.9 per cent. There were no deaths following 94 resections for duodenal ulcer.

(5) A two-stage resection of the stomach for selected cases of duodenal ulcer is discussed.

(6) The technic used in teaching subtotal resection of the stomach for duodenal ulcer to the Resident Staff on the West Surgical Service at the Massachusetts General Hospital is described.

(7) The importance of the antral mucosa in gastric physiology, as related to surgery for duodenal ulcer, is stressed.

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DISCUSSION—DR FORDYCE B ST JOHN, New York When Doctor McKittrick asked me to open the discussion on this paper, I was delighted, as I think it brings up an important point in gastric surgery

To any surgeon who has spent considerable time in the region of the posterior wall of the first part of the duodenum and between it and the head of the pancreas in inflammatory lesions, this paper strikes a sympathetic note

Too much has been written illustrating man's ingenuity in anastomosing stomach and jejunum and too little by experienced observers on the problem of the duodenal stump, frequently the only really difficult part of a gastric resection

For these reasons one welcomes this paper which directs attention and consideration to this important step in the procedure

The authors first studied 179 primary resections in a five-year period Of these, 55 were for gastric ulcer, 124 were for duodenal ulcer There were ten deaths, an operative mortality of 8.1 per cent in the latter series Peritonitis occurred in nine instances, in seven it was due to leakage from the duodenal stump Five of these cases died None died in the gastric ulcer series The comparison seemed significant

Fully aware of the technical difficulties frequently associated with dissection and closure of the duodenal stump, and especially with compromised tissue, the authors have proposed, in difficult cases, the two-stage procedure designed to diminish the operative risk

In support of this thesis, a report has been submitted summarizing the results of the past two years at the Massachusetts General Hospital One hundred and forty-five primary resections are included, 51 for gastric ulcer, with two deaths, and 94 consecutive resections for duodenal ulcer, without an operative death This latter series in a general hospital with a constantly changing resident staff and during the past two trying years represents, indeed, an achievement An operative mortality of approximately four per cent in the 51 cases of gastric ulcer is nearer the average experience of other clinics, especially where advanced lesions and those suspected of being cancer are attacked in all age-groups However, the fact that in the first 55 gastric ulcers reported there was no death and in the latter series of 51 there was a mortality of four per cent shows the difficulty of drawing conclusions from statistics alone

Furthermore, it is to be noted that 63 classical one-stage subtotal gastrectomies were carried out for duodenal ulcer, with no death during the past two years, whereas, there has been an opportunity for only 23 two-stage procedures during the same period, also with no deaths Therefore, from the record alone one is not justified in drawing conclusions as to the actual value of the method proposed

The results on both Dr Arthur Allen's and Doctor McKittrick's services have been highly satisfactory whether the classical one-stage operation, the one-stage, with the removal of antral mucosa, or the suggested two-stage procedure has been carried out

## GASTRECTOMY FOR DUODENAL ULCER

In order to broaden the basis of comparison and add to the material for discussion, I shall present a summary of the results in a general hospital over almost the same period of time. Time, since receiving Doctor McKittick's paper, did not permit subdivisions into gastric and duodenal groups (Tables I, II and III)

TABLE I  
PEPTIC ULCER

200 PRIMARY RESECTIONS OF THE STOMACH FOR PEPTIC ULCER 1939-1943 (INCLUSIVE)

*The Presbyterian Hospital  
New York City*

Operation	Cases	Deaths	Mortality
Subtotal gastrectomy	200	8	4%

TABLE II  
PEPTIC ULCER

FATAL COMPLICATIONS FOLLOWING 200 SUBTOTAL RESECTIONS OF THE STOMACH

1939-1943 (INCLUSIVE)

*The Presbyterian Hospital  
New York City*

Peritonitis (due to leakage of duodenal stump)	3
Pulmonary	2
Hemorrhage	0
Malfunction of stoma	0
Miscellaneous	3
1 Thrombosis of celiac axis and superior mesenteric artery	
1 Gangrene of transverse colon (compromised blood supply)	
1 Cerebral accident	
Total	8

TABLE III  
PEPTIC ULCER

99 PRIMARY RESECTIONS OF THE STOMACH FOR PEPTIC ULCER

1942-1943 (INCLUSIVE)

*The Presbyterian Hospital  
New York City*

Operation	Cases	Deaths	Mortality
Subtotal gastrectomy	99	3	3%

### CAUSE OF DEATH

Peritonitis (due to leakage of duodenal stump)	2
Cerebral accident	1

### CONCLUSIONS

A critical review of the paper under discussion as well as of our own experience, would lead one to make the following observations

1 Peritonitis as a cause of death following subtotal gastrectomy is more frequent than is generally appreciated

2 Leakage from the duodenal stump is by far the most common cause of peritonitis. The practice of using a soft rubber tissue drain down to the region of, but not in contact with, the closure has saved lives in our clinic by establishing in the event of leakage, a temporary duodenal fistula, and, thus, preventing spreading peritonitis. It must be noted, however, that this factor has failed in the fatal instances reported. We are opposed to the use of a stiff rubber tube.

3 Leakage may be due to two main factors

a Local conditions actually at the site, such as acute inflammatory reaction, compromised wall of duodenum and actual perforation causing technical difficulties, and



b Leakage may be due also to any factor which causes back pressure in the afferent loop from the duodenal stump to the gastrojejunal anastomosis

4 It has been our custom, also, in a few selected cases, especially in the most acute phase, to avoid dissection of the ulcer-bearing area. In these instances, the antral mucosa is always removed before the antral stump is inverted.

5 A two-stage procedure is suggested to add to the safety factor in gastric resection in difficult cases of duodenal ulcer. Its advantages are obvious and have been presented clearly.

Its disadvantages, aside from the economic and psychologic, are doubling the number of anesthetics and abdominal operations for a given lesion which, of necessity, must be performed in all age-groups.

6 Finally, I should feel that Doctor McKittrick, and his associates, have made an interesting suggestion. That it will add a safety factor seems evident but whether it will prove to be a wiser course to follow than those now in use must depend on further factual evidence.

DR HENRY F GRAHAM, Brooklyn. Doctor St John briefly mentioned, in passing, the one most important factor in this whole discussion, when he said that in difficult cases they have not tried to remove the ulcer.

That is where all the trouble occurs. At the Methodist Hospital we have recently had an analysis made of our work in gastric resection for peptic ulcer from 1936 to date. We have not divided it into duodenal and gastric. In the first four years of this period the mortality was so high that I hate to mention it. I myself lost a couple of cases in an attempt to remove the duodenal ulcer, but during the past four years, commencing January 1, 1940, up to date, we have had 77 such operations, with one death. That one fatality, if we compare it with Doctor McKittrick's statistics, should have been eliminated because it was due to a massive hemorrhage operated upon within 48 hours of the onset of bleeding. I think he said he excluded these in his series.

We attribute the improved mortality to a number of different factors—better anesthesia, better preparation, *etc.*, but the chief improvement in mortality is due to the fact that we have ceased trying to remove the duodenum in cases where it is difficult.

To date we have a pretty complete follow-up. This follow-up is as complete as it was possible for us to make it up to December, 1943, and we have no evidence to prove to us at all that leaving the duodenal ulcer behind is a source of future trouble to the patient where a subtotal resection has been done.

If we find it difficult to remove the duodenum, we do not hesitate to leave several inches at the pylorus of the stomach, remove the mucosa, pass a finger down through to gently dilate the pylorus and then invert this portion of the pylorus which has been left, with a couple of nonabsorbable sutures, into the duodenum.

I suppose it is really unnecessary for me to mention it, but at one hospital, with which I was formerly connected, I saw two autopsies where death was due to blowing out of the duodenal stump because they had used catgut to sew the duodenal end up. I do not think anybody uses that now.

There is only one other type of case we have to consider, then, those with massive hemorrhage and repeated hemorrhage from a duodenal ulcer. It is not safe to leave the untreated ulcer behind because of the hemorrhage.

Doctor Pfeiffer mentioned one way of handling that situation. In one such case that I have had, it was handled in a little different way, quite successfully, and without further trouble. (Demonstration on blackboard.) This is the duodenal stump. The ulcer is here on the back wall of the duodenum with the vessel in the center of the ulcer. A nonabsorbable suture was passed deep through the base of the ulcer with a cutting needle. Then this tongue-shaped flap from the anterior wall was turned over so the peritoneal surface was brought against the base of the ulcer, and the suture was tied down to hold the flap against the base of the ulcer. A reconstruction was done at the end of the

duodenum with the usual nonabsorbable sutures, and it was completely closed without any excessive difficulty

It seems to me that a little ingenuity in the care of the duodenum, and less attempt to take it out, will pay big dividends in these cases. I may say that these 77 operations we had were performed by twelve different operators, so it is not a question of any one individual's dexterity.

In commenting on Doctor McKittrick's paper, it would seem to me that even if he were going to leave the pylorus behind for a second operation, it would not be necessary to transect the stomach twice, as he showed in one of his diagrams, first near the pylorus and up again higher, where the section was done for anastomosis. His original section could have been done up near the anastomosis, and the pyloric end could have been turned down, and then, if he decided to leave the pylorus later, the second section could have been made.

There will be many cases where you will decide to take the ulcer out, or will go down to the duodenum, so two sections above will be unnecessary.

DR RALPH COLP, New York. Subtotal gastrectomy has been the operation of choice in our clinic since 1923. Six years ago a new group of surgeons was assigned to take care of ward patients admitted to the Gastric Service in the hospital. I would like to show three slides which emphasize quite clearly, I think, that the crux of the operation of subtotal gastrectomy really centers about the closure of the duodenum.

In this particular series, which is divided into two three-year periods, certain changes were gradually made in technic in an effort to lower the morbidity and the mortality. There were only three cases in which a prepyloric "*auschaltung*," as recommended by Finsterer, was done. Inasmuch as the follow-up in these cases was not good, we decided to eliminate, if possible, this particular procedure.

TABLE I  
ANALYSIS OF DEATHS IN SUBGROUPS  
Series A

	No of Cases	No of Deaths	Cause of Death	Mortality Rate
Group A Duodenal ulcer	48	3	(1) Cerebral thrombosis (2) Generalized peritonitis (3) Alkalosis	6.25%
Group B Bleeding duodenal ulcer	16	3	(1) Duodenal dehiscence Generalized peritonitis (2) Hemorrhagic broncho-pneumonia (3) Subphrenic and subhepatic abscesses	18.75%
Group C Previously perforated duodenal ulcer	15	2	(1) Massive atelectasis (2) Pneumonia after drainage of subphrenic abscess	13.33%
Total	79	8		10.13%

In Series A (Table I), during the first three years, there were 79 cases of duodenal ulcer, which included (A) the duodenal ulcers with intractable pain and some with pyloric stenosis, (B) those which had bled, and (C) those in which a perforation had previously occurred.

There were 48 cases in Group A with three deaths. One was caused by a cerebral thrombosis. One was due to a generalized peritonitis from a duodenal leak, and the third was caused by an alkalosis due to atomy of the stomach from which the patient vomited persistently. At the end of about two weeks, an entero-anastomosis was done without any relief. Then jejunostomy was finally instituted when it was too late. This case, and others in which we experienced trouble with gastric emptying, due not only

to an atomy of the stomach but possibly to an obstruction at the stoma, caused us subsequently to frequently institute jejunal alimentation at the time of the primary operation (See Table III)

In the second group (B) consisting of 16 cases of bleeding duodenal ulcer, there were three deaths. One was due to duodenal dehiscence, with generalized peritonitis, another was caused by a hemorrhagic bronchopneumonia, and a third was traced to a subphrenic and subhepatic abscess which came from a duodenal leak.

There were 15 cases which had previously perforated (Group C). There were two deaths, one from a massive pulmonary atelectasis, and the second from a pneumonia, after the drainage of a subphrenic abscess.

Most of these cases had postmortem examinations, which account for the causes of death which are herewith given. So, in the total of 79 cases in Series A, there were eight deaths, or 10.13 per cent, in which four could be attributed to a dehiscence of the duodenal stump.

TABLE II  
ANALYSIS OF DEATHS IN SUBGROUPS  
Series B

	No of Cases	No of Deaths	Cause of Death	Mortality Rate
Group A Duodenal ulcer	67	3	(1) Hepatitis and pneumonia (2) Pulmonary embolism (3) Diffuse bronchopneumonia	4.48%
Group B Bleeding duodenal ulcer	16	1	(1) Duodenal dehiscence Subhepatic abscess	6.25%
Group C Previously perforated duodenal ulcer	11	0		0
Total	94	4		4.26%

In the second series, B, consisting of 94 cases, there were 67 cases (Group A) of duodenal ulcer with three deaths. Autopsy disclosed that one patient succumbed from a hepatitis, evidently due to sulfanilamide, which had been given for a pneumonia, one from pulmonary embolism, and a third from a diffuse bronchopneumonia.

In the bleeding ulcer cases (Group B) there were 16 cases with one death, due to a duodenal dehiscence, resulting in a subhepatic abscess. I think the reason for the diminution in the mortality of the second group of the bleeding duodenal ulcers might be attributed to the fact that we no longer operate upon these duodenal ulcers immediately. Whenever possible, we wait three weeks after the hemorrhage has ceased, during which time these patients have adequately regained their strength, and their blood proteins and hemoglobin have approached more normal limits.

TABLE III

	Series A July 1 1937 to June 30 1940	Series B July 1, 1940 to June 30 1943
Number of cases	79	94
Mortality	8	4
Mortality percentage	10.13%	4.26%
Drainage of duodenal stump	29	72
Antecolic type of gastrojejunostomy	35	91
Retrocolic type of gastrojejunostomy	44	3
Jejunostomy	4	32
Spinal anesthesia	16	84
General anesthesia	63	10

## GASTRECTOMY FOR DUODENAL ULCER

In Group C, 11 cases in which perforation had previously occurred, there was no mortality

Therefore, in Series B, the gross mortality was 4.26 per cent

Aside from the increased skill of the operators in causing a diminution in the mortality between Series A and Series B, we feel that other factors may have entered into this reduction of the mortality (Table III)

First of all we are instituting drainage of the duodenal stump with increased frequency. We use a rubber dam drain which is placed down into the vicinity of the sutured duodenum and brought out through a right subcostal stab

In these cases which were drained, there were 13 that had bile-stained dressings, but in this group there were only two cases which developed a generalized peritonitis. In those cases in which the duodenal drainage was profuse, the aspirated contents were introduced through the jejunostomy, maintaining the chemical balance. We believe with Doctor St. John that drainage does no harm.

As far as the types of anastomosis are concerned, you can see we are doing more and more of the antecolic type of anastomosis. We found no immediate or late differences between the antecolic and the retrocolic type. We found that the antecolic is a simpler technical procedure, and in the event a patient subsequently develops a gastrojejunal ulcer, a secondary gastric resection is not as difficult as if a retrocolic anastomosis had been made.

We have used more spinal anesthesia during the past three years, but, unfortunately, we have noticed no diminution in the incidence of pneumonia, which, in Series B, was responsible for three of the four mortalities.

DR. DONALD C. BALFOUR, Rochester, Minn. Doctor McKittrick's presentation illustrates the fact that surgery of the stomach has reached a level of which the surgeons of this country can be proud. In the surgical treatment of ulcer of the duodenum, Doctor McKittrick has given emphasis to the problems involved in the direct attack on the ulcer. Since it is not always advisable to remove a lesion situated on the posterior wall, if the removal of such a lesion introduces considerable risk to the operation, one should keep in mind that an indirect procedure will bring about healing of the ulcer. As a matter of fact, it is a principle in gastric surgery that any operation which has ever been designed for treatment of peptic ulcer—where it is partial gastrectomy or gastro-enterostomy—is based on physiologic principles.

One suggestion which has interested me was that of the reintroduction of the principle of partial gastric exclusion. You are all familiar with the history of that procedure. I had the pleasure of seeing Sir Hugh Devine perform a number of such operations in 1935, and they accomplished one principle very definitely, namely, that any procedure which circumvents the duodenum will bring complete healing of any lesion which may be present there. It would seem reasonable that every advantage should be taken of the fact that exclusion of the gastric contents from the duodenum will solve the problem of curing the duodenal ulcer, and that unnecessary risk in removing inflammatory processes in the duodenum should be avoided.

All in all, I believe that this whole question of peptic ulcer should be introduced into the program each year, for it is a changing scene and we know little about the effect of these physiologic operations.

I should like to ask Doctor McKittrick one question in view of the higher incidence of recurrent ulcer when the pyloric stump is not removed. What does he consider the desirable interval of time between the first and second stages of this operation? We have all known cases in which recurrent ulcers have apparently developed very soon after either gastro-enterostomy or partial gastrectomy.

DR. WILLIAM F. RIENHOFF, JR., Baltimore, Md. I was very much interested in Doctor McKittrick's excellent paper, which he presented so well, and in the various dis-

cussions that have preceded this one. It is unfortunately true in all branches of surgery that in the course of training of a Junior Staff in all clinics there will occur technical errors that can only be avoided by repetitious and continuous operative experience. This is the price that must be paid for the training of a surgeon and it is, of course, most desirable to keep the price as low as possible. However, I believe that it is not quite fair to judge an operative procedure by the inclusion of the Junior Staff results with those of the Senior Staff, for in so doing there will be included operative deaths, or at least operative complications, which should not necessarily be attributed to the operative procedure, but, as I stated, to the inexperience of the younger surgeon.

Since 1939, when I presented before this society a series of cases which had been operated upon for peptic ulcer of the pylorus and duodenum, a one-stage resection of the stomach has been employed. A conservative resection of the stomach has been performed in a series of 189 consecutive cases and in only seven, or approximately four per cent, has it been necessary to reoperate upon the patient for the development of a jejunal ulcer at or near the site of anastomosis. After conservative resection the continuity of the gastro-intestinal tract has been reestablished by a short-loop antecolic gastrojejunostomy.

It is difficult in different individuals to be sure of the amount of stomach which has been resected, but as near as one can estimate I would say that what has been considered a conservative resection would be about one-third to one-half of the stomach, including some of the fundus, the pyloric antrum, pylorus and first part of the duodenum. It is believed preferable to perform this operation in one stage, and that it is unnecessary in the great majority of patients to resect more than this amount of the stomach.

This series of cases has been studied from both the standpoint of immediate and remote postoperative course. In this series there have been no deaths from operation and no postoperative complications that could in any way be attributed to leakage of the duodenal stump. There have been no cases of duodenal fistula. This study has brought out certain interesting points that have impressed me. In the first place, in practically all of the cases there has been evidence of multiple ulcerations of the duodenum. On the anterior, superior and posteromedial surfaces there have been either visible scars or palpable ulcerations. In some instances the duodenum has been actually ligneous from multiple ulcerations making it sometimes technically quite difficult to close the duodenal stump. Another interesting feature is that the great majority of these patients have had bleeding of greater or less severity and in all these there has been a perforating ulcer into the head of the pancreas. The majority of these have been on the posteromedial surface of the duodenum at about the junction of the first and second portion. In some the perforation has been lower down in the second or descending portion. Closure has been satisfactory in every one of the cases, but more difficult in some than in others. It is our impression that it makes very little difference whether or not the ulcer is resected, that if the duodenum is turned in and the gastric contents shunted away from the ulcer bearing portion of the duodenum, that is that portion above the ampulla of Vater, that the ulcers will heal. In only three cases has there been bleeding after resection, and in these complete recovery occurred without further surgical intervention.

The type of closure of the duodenum has been simple suture of the amputated stump with interrupted silk or cotton sutures.

In the more recent cases the duodenum has not been clamped across with a Payr crushing clamp, but merely amputated, bleeding points clamped and interrupted sutures used throughout to turn in the cut edge. This avoids, of course, the use of a continuous catgut suture and the turning in of devitalized tissue. The duodenum has been turned in so that all that portion that has been mobilized and freed from the head of the pancreas is intussuscepted, so to speak, into the lumen of the intestine. The reason for this is that sometimes the circulation of the stump may be slightly jeopardized due

## GASTRECTOMY FOR DUODENAL ULCER

to separation of the intestine from the head of the pancreas and to avoid any possibility of interference with healing this portion should not be allowed to remain free in the peritoneal cavity. If, after turned in, some of it should become necrotic it will drain into the intestinal tract.

I would like to show two slides which demonstrate the method of closure employed. Closure of the duodenum that is the site of peptic ulcer is of course more difficult than closure of the duodenum which is uninvolved as in peptic ulcer or malignant ulcer of the stomach. It is well, as I stated above, not to use a crushing clamp, because often times this uses up quite a bit of the available duodenum for turning in. As shown by the slides, the vertical closure of the duodenum is most satisfactory, providing there is enough of the first or beginning of the second portion above the ulcerated area to give a satisfactory amount to turn in, but if the duodenum is very heavily scarred, due to a perforating ulcer into the pancreas, less of the medial wall of the bowel will have to be mobilized if the closure is begun medially and proceeds laterally rather than the vertical closure, *i.e.*, closing from the midline out. This has proved to be a most gratifying procedure, lessening the necessity of mobilizing so much of the scarred portion of the duodenum normally adjacent to the head of the pancreas. Mobilization of the duodenum too far down the second portion is thought to be inadvisable, because of possible injury to the common duct or interference with the circulation of the duodenal stump.

Drainage of the duodenal stump is strictly avoided. If the duodenum is turned in correctly, the circulation has not been jeopardized, draining is unnecessary, and it only invites infection and the possibility of the formation of a fistula. Drainage of the peritoneal cavity following resection of the stomach is studiously avoided.

One difficulty that has been mentioned in previous papers, namely, increased pressure in the afferent loop, is felt to be due either to improper suture of the afferent loop to the lesser curvature where constriction of the lumen may be produced, or in those cases of retrocolic gastrojejunostomy in which the transverse mesocolon has caused a constriction of the afferent loop. The antecolic jejunostomy is preferred, first, because the danger of constriction of the transverse mesocolon is avoided, second, the afferent loop of jejunum is just as short if the colon and omentum is displaced to the left, and, third, because in that small percentage of cases in which jejunal ulcers occur reresection is far less difficult to perform following antecolic rather than a retrocolic gastrojejunostomy.

DR. L. S. MCKITTRICK (closing). I am deeply grateful to the discussers for their contributions to this problem. I just want to make clear that in this condensed presentation we probably may have given the wrong impression in overemphasizing the two-stage procedure.

Our primary interest is the elimination of those complications arising from the duodenal stump following subtotal resection for duodenal ulcer.

In answer to Doctor Balfour's question, of course, we are fully aware, and fearful, of the development of a marginal ulcer. We like to undertake the second stage at as early a time as we can. The longer the patient waits the easier it is, so we have performed these operations in periods varying from three to six or eight weeks depending upon the severity of the inflammatory reaction in relation to the ulcer at the time of the primary operation.

# CLOSURE OF COLONIC STOMA

## IMPROVED RESULTS WITH COMBINED SUCCINYLSULFATHIAZOLE AND SULFATHIAZOLE THERAPY\*

CLAUDE F DIXON, M D ,

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AND

RAYMOND E BENSON, M D

FIRST ASSISTANT IN SURGERY, MAYO CLINIC

ROCHESTER, MINN

THE RESULTS OF CLOSURE of colonic stomas always have been unsatisfactory in a rather high percentage of cases. This procedure necessarily has to be carried out in a field that is contaminated with many bacteria. In the past, wound infection frequently has followed closure of a colonic stoma. In many cases, extensive abscesses have formed in the subcutaneous tissues, the edges of the skin have become undermined, and multiple draining sinuses have made the patient a semi-invalid for weeks or months. Even more distressing than these complications, in some cases, has been the resumption of fecal drainage from the wound. Since we have been using a combination of succinylsulfathiazole and sulfathiazole in the treatment of persons subjected to surgical closure of colonic stomas, the incidence of these complications has been lowered remarkably.

### MATERIAL

This paper is based primarily on 102 consecutive cases (Group 1) in which succinylsulfathiazole and sulfathiazole were employed while the patients were hospitalized for closure of colonic stomas. In order to obtain an unbiased evaluation of the results of this treatment, three other groups of cases have been considered. In each of these three groups of cases the patients were hospitalized for closure of colonic stomas and, with the exception of the administration of the sulfonamides, the treatment was the same as that employed in Group 1. Group 2 includes 102 consecutive cases in which no sulfonamide drug was used. Group 3 includes 40 cases in which only sulfanilamide was employed. Group 4 embraces 30 cases in which only sulfathiazole was administered.

### TREATMENT EMPLOYED IN CASES OF GROUP 1

After the spur of the colonic stoma had been eradicated by application of clamps, and sufficient time had elapsed to allow all edema and induration at the site of the stoma and in the surrounding tissues to subside, the stoma was considered ready for closure.

*Preoperative Treatment*—The patients routinely were hospitalized for three full days (72 hours) before the stoma was closed. As soon as they had been admitted to the hospital a nonresidue, high carbohydrate diet was prescribed and the oral administration of succinylsulfathiazole was started. We have standardized the dose of this drug even though there is good evidence that the effect of the drug varies considerably among different patients. In the

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\* Read before the American Surgical Association, May 3-4, 1944, Chicago, Ill

## CLOSURE OF COLONIC STOMA

case of an adult, 4 Gm of the drug was administered as soon as the patient had been admitted to the hospital. This dose was repeated every four hours until six doses (24 Gm) had been given. Thereafter, a dose of 2 Gm was administered every four hours (12 Gm in 24 hours), the last dose was given approximately six hours before the operation was performed.

The proximal and distal loops of colon were irrigated daily with warm tap water for three days before the operation. The irrigating was done through the colonic stoma and through the rectum. The final irrigation was done 24 hours before the operation was performed. During the 24 hours before the

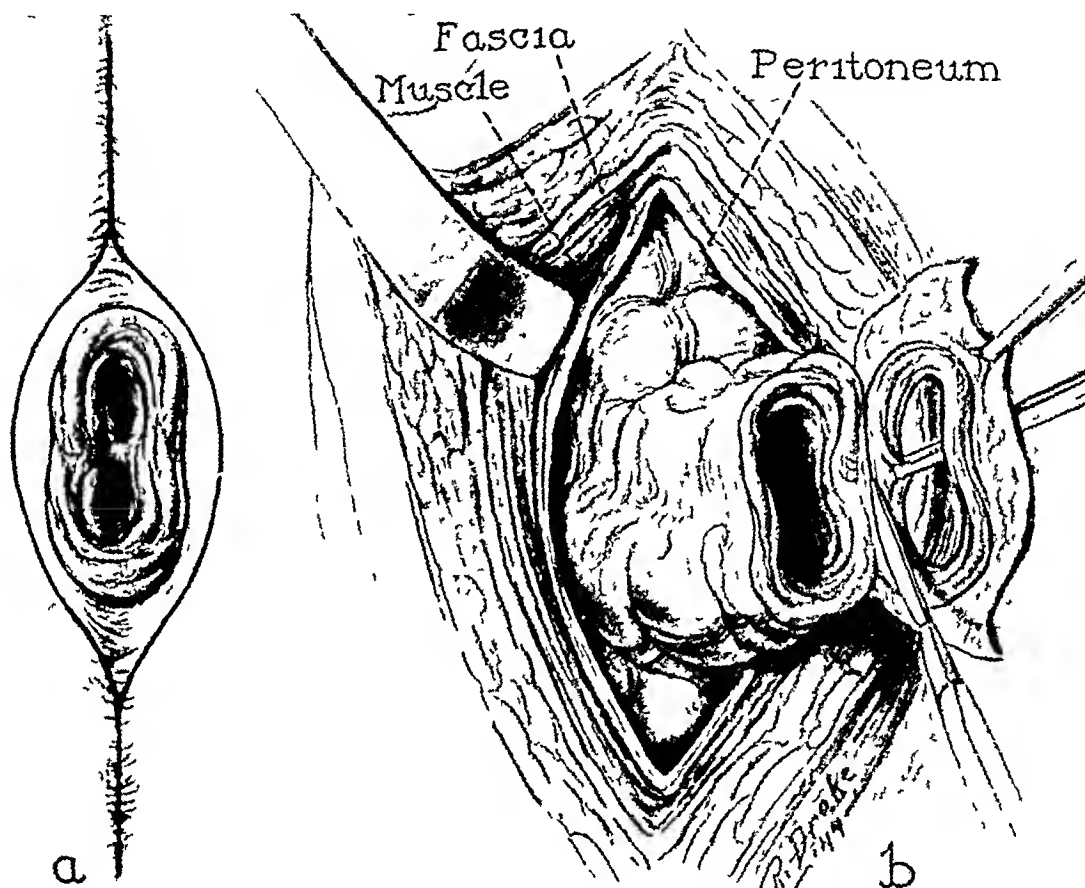


FIG 1—Closure of colonic stoma. *a* Incision in skin encircling the stoma. *b* The fascial, muscular and peritoneal layers have been incised and the proximal and distal limbs of colon are mobilized. The previously encircled layer of skin and subcutaneous tissue is being excised from the wall of the bowel. The edges of the colonic stoma are freshened by excising a narrow margin of it.

operation, two drachms (8 cc) of camphorated tincture of opium were administered every four hours, and any fluid that had been retained in the proximal or distal segments of the colon was removed by aspirating through the colonic stoma and through the rectum with a large bulb syringe. The last dose of camphorated tincture of opium was administered approximately eight hours before the operation. The last aspiration also was performed about the same time.

*Surgical Treatment*—An incision was made on each side of the stoma passing through the scar produced by the previous operation. These incisions were joined so as to encircle the stoma. Then the colon was freed from the anterior abdominal wall at the site of the stoma (Fig 1). The deep fascia was



next cleansed of fat and scar tissue sufficiently to form a definite layer which subsequently could be approximated to restore the strength of the abdominal wall. This fascia then was incised. In all cases the peritoneum was then opened and the two limbs of colon mobilized sufficiently to allow accurate approximation (Fig 1). Immediately adjacent to the peritoneum, one frequently encounters a thin layer of adhesions which have "walled-off" the site of the stoma from the main peritoneal cavity. When these adhesions were

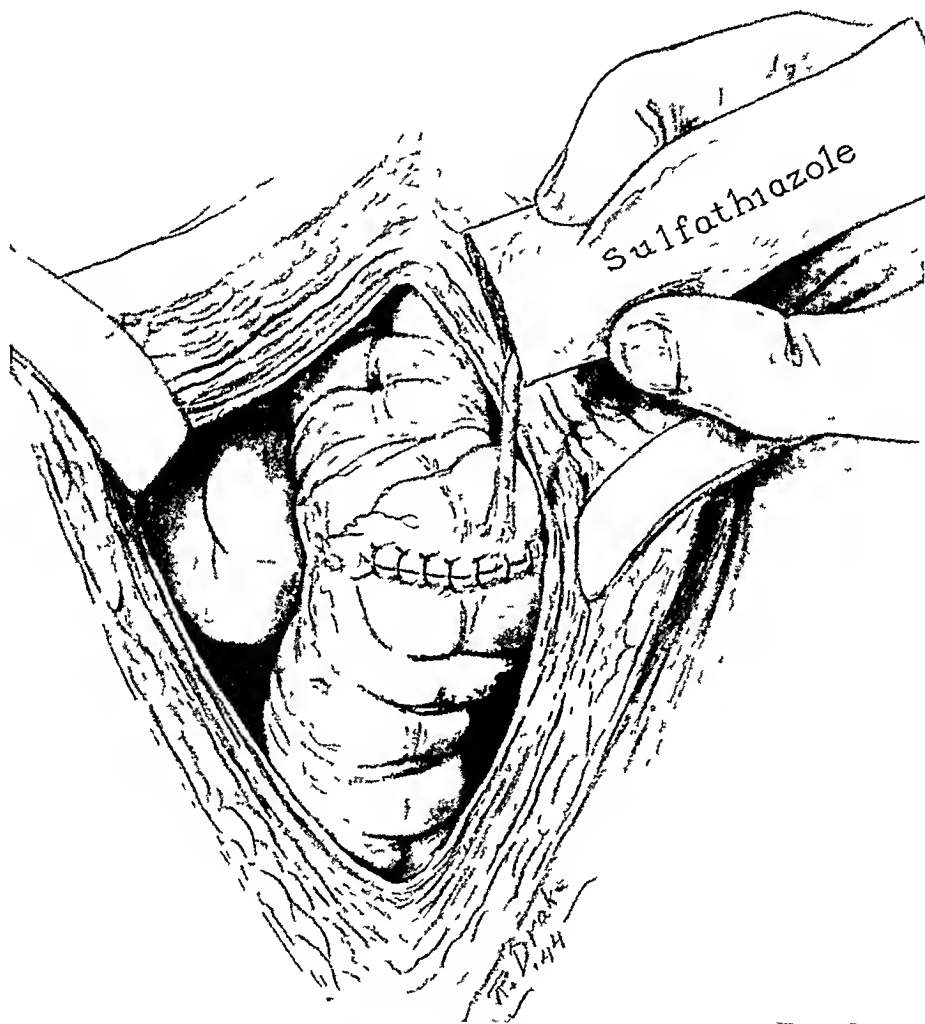


FIG 2—The stoma has been closed transversely to the long axis of the bowel. The completed anastomosis is dropped back inside the peritoneal cavity and 5 Gm. of sulfathiazole inserted.

encountered, they were not disturbed unnecessarily. The previously encircled cuff of skin and subcutaneous tissue then was excised from about the stoma. The edges of the stoma were freshened by excising a narrow margin and the colonic opening was closed transversely to the long axis of the bowel with two layers of running chromic catgut sutures. Additional interrupted catgut sutures were inserted in some cases. In a few cases, the mesial edges of the intestine had not united to form the usual colonic spur, consequently, the spur could

## CLOSURE OF COLONIC STOMA

not be crushed preoperatively and it was necessary to separate the proximal and distal loops of the colon and perform a complete end-to-end anastomosis. The anastomosis being completed, the colon was dropped back into its normal position within the peritoneal cavity (Fig 2)

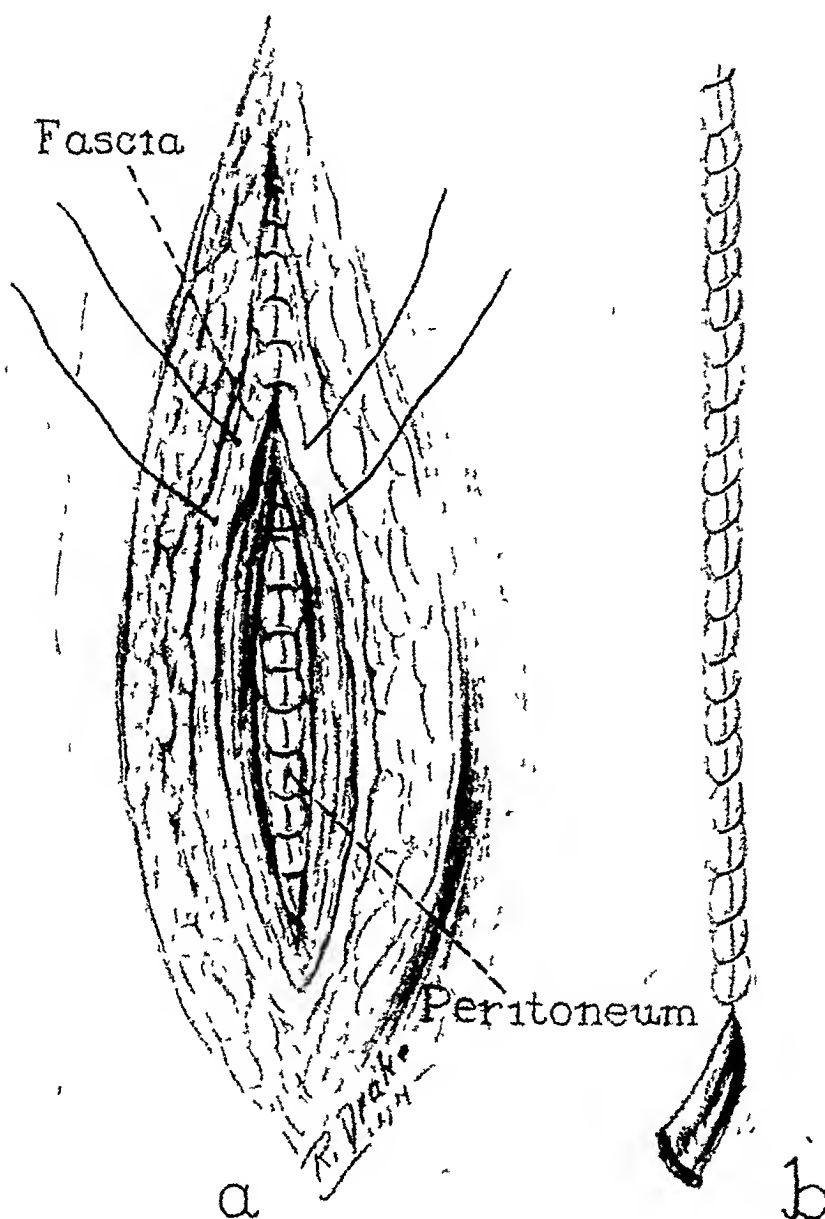


FIG 3—*a* The peritoneal, muscular and fascial layers are closed with a running suture *b* A Penrose drain and a few grains of sulfathiazole are placed in the subcutaneous layer. The skin is closed.

Sulfathiazole powder was dusted intraperitoneally around the site of closure. Five grams were so administered routinely, but in occasional instances in which the subperitoneal space about the site of closure was small, lesser amounts, that is as little as 2.5 Gm., were used.

The peritoneal, muscular and fascial layers, which had previously been dissected free, were then closed tightly with surgical gut sutures (Fig 3). Fifteen to 30 grains (1 to 2 Gm.) of sulfathiazole were dusted into the super-

ficial fatty layer In most cases a small Penrose drain was inserted subcutaneously The skin was closed snugly with a running suture of plain catgut If the subcutaneous fatty layer was thick, a few retention sutures of braided silk were inserted to obliterate any potential dead space

*Postoperative Treatment*—Sulfonamide therapy was not employed postoperatively Only small amounts of water, that is 15 to 30 cc every four hours, were administered orally until flatus was passed freely from the rectum In the average case, this was on the second or third day after operation The diet then was increased gradually until the fifth or sixth day after operation, when a full diet was permitted A large lubricated rubber tube was inserted into the rectum periodically in order to prevent pressure by retention of gas or feces The operative wound received no special care except the routine application of dressings The Penrose drain was removed on the fourth or fifth day after the operation

#### TREATMENT EMPLOYED IN CASES OF GROUPS 2, 3 AND 4

In these groups there was no preoperative use of sulfonamides In Group 2 (102 cases), as has been said, sulfonamides were not used at all In Group 3 (40 cases) sulfanilamide, and in Group 4 (30 cases) sulfathiazole was dusted about the site of closure at operation In other respects, including the preoperative treatment, the surgical technic and the postoperative regimen, treatment in these groups was the same as in Group 1

Usually the quantity of sulfanilamide or of sulfathiazole applied locally, respectively, in Groups 3 and 4, was 5 Gm In an occasional case, however, in which the subperitoneal space about the anastomosis was small, a lesser amount, as little as 2.5 Gm of the powder under consideration, was employed

#### RESULTS

In the cases in Group 1, namely, the 102 cases in which a combination of succinylsulfathiazole and sulfathiazole was employed, the incidence of wound infection and of recurrence of fecal drainage was remarkably low In the majority of cases the wounds healed by primary intention An extensive subcutaneous abscess did not occur in any case, and a resumption of fecal drainage from the wound occurred in only two cases (Table I) The postoperative febrile reaction was slight or minimal and in most of the cases the average time that was required for the intestine to resume its normal function was shorter than it was in the cases in Group 2, that is, in the 102 cases in which no sulfonamide drug was employed In the usual case, as has been said, the patient was able to expel flatus freely from the rectum on the second or third day after the operation and normal bowel movements were resumed on the third or fourth day In general, convalescence was remarkably easy and free of complications

In marked contrast with the good results obtained in Group 1 are the distressing sequelae that frequently occurred in Group 2 (Table I) Spontaneous fecal drainage from the wound following surgical closure occurred in 31 cases,

CLOSURE OF COLONIC STOMA

or 30 per cent of the cases in this group. It occurred in only two of the 102 cases in Group 1. In some cases these postoperative fecal fistulae closed spontaneously, but in others they had to be closed by a secondary operation. In all cases in which a fecal fistula occurred it was a distressing complication which delayed complete recovery for weeks or months. Extensive wound infections were common before the advent of the sulfonamides. Moderate or severe infection of the wound occurred in 86 (84 per cent) of the cases in Group 2 in which no sulfonamides were used. In the cases of Group 1, however, wound infection developed in only 13, or 13 per cent of cases, and in only one case did extensive subcutaneous abscesses and undermining of the skin occur. In 82, or 80 per cent of the cases in Group 1, the wound had healed firmly by the fourteenth postoperative day, healing in a similar period was observed in only eight (8 per cent) of the cases in Group 2. The better results obtained in the cases in Group 1 must be attributed to the use of succinylsulfathiazole and sulfathiazole, as the treatment in the two groups of cases was the same in all other respects.

Sulfanilamide, as has been explained, was applied locally in the 40 cases in Group 3. Although the results were slightly better than those obtained in Group 2, namely, the 102 cases in which no sulfonamide drug was employed, they still were poor (Table I). Spontaneous fecal drainage from the wound

TABLE I  
CLOSURE OF COLONIC STOMAS  
COMPARISON OF RESULTS WITH VARIOUS FORMS OF TREATMENT

Group	Treatment	Total Cases	Infected Wounds Per Cent	Resumption of Fecal Drainage, Per Cent	Wound Healed by 14th Postoperative Day, Per Cent
1	Succinylsulfathiazole and sulfathiazole	102	13	2	80
2	No sulfonamides	102	84	30	8
3	Sulfanilamide locally	40	77	25	10
4	Sulfathiazole locally	30	63	17	20

occurred in ten (25 per cent) of the 40 cases. Healing of the wound by the fourteenth day was observed in only four, or 10 per cent, of the cases. Wound infection occurred in 31 (77 per cent) of the cases.

Again, as has been related, sulfathiazole was applied locally in the 30 cases in Group 4. The results obtained in this group were somewhat better than those secured in Group 3, but they did not approach those that ensued in Group 1, that is, in the 102 cases in which a combination of succinylsulfathiazole and sulfathiazole was used. Spontaneous fecal drainage from the wound occurred in five, or 17 per cent, of the 30 cases. In six, or 20 per cent, of the cases the wounds had healed by the fourteenth postoperative day. Wound infection remained common and occurred in 19, or 63 per cent, of the cases.

In the 102 cases in Group 1 no deaths occurred in the hospital. In the 102 cases in Group 2, there were three postoperative deaths. Two were attributed to pulmonary embolism, the third resulted from peritonitis and pulmonary embolism. In the 40 cases of Group 3 there was one death in the hospital and

that was due to gangrenous cholecystitis. In the 30 cases of Group 4, one patient died from postoperative intestinal obstruction and peritonitis.

It is, thus, apparent that the results in the cases (Group 1) in which a combination of succinylsulfathiazole and sulfathiazole was used not only were better than those obtained in the cases (Group 2) in which no sulfonamide drug was employed but also were better than the results obtained in the cases (Groups 3 and 4) in which sulfanilamide or sulfathiazole was applied locally.

COMMENT—Succinylsulfathiazole is the succinyl salt of sulfathiazole. Chemically, it is 2-(N<sub>4</sub>-succinyl-sulfanilamido)-thiazole. It contains, in addition to the succinyl radical, a free carboxyl group<sup>1, 2, 3, 4</sup>. When it is administered orally it is absorbed from the bowel in only very small amounts. Poth and Knotts<sup>4, 5</sup> found that, on an average, only five per cent of the ingested drug was excreted by the kidneys. The majority is retained in the lumen of the intestine where it markedly reduces the number of coliform bacteria in the intestinal content. Sulfathiazole, on the other hand, is absorbed rapidly from the gastro-intestinal tract and while it has some effect on the intestinal bacterial flora this action is not pronounced.<sup>5</sup> When placed locally in wounds, it exerts a powerful bacteriostatic effect without apparent injury to the surrounding tissues. The favorable results obtained with these two drugs in the cases in Group 1 apparently has been due to their ability to inhibit the growth of the many infectious organisms found in the large intestine.

*In vitro*, succinylsulfathiazole has little or no activity against strains of *Escherichia coli*. When the drug enters the intestinal tract and comes in contact with the intestinal mucosa, however, it evidently becomes a highly effective bacteriostatic agent. It has been shown that succinylsulfathiazole when administered orally may cause the number of coliform bacteria to become negligible. Thus it has been shown<sup>6</sup> that specimens of stools obtained from various human beings, and which contained 10<sup>6</sup> to 10<sup>10</sup> organisms per gram of wet stool before the administration of succinylsulfathiazole was started, contained 0 to 500 or 700 organisms per gram of wet stool after therapy with this drug. How this drug, which is ineffective in the test tube, exerts such a profound influence *in vivo* has not been well established. Poth and Knotts<sup>6</sup> have speculated that "succinylsulfathiazole must \* \* \* be converted into a more active compound, probably sulfathiazole. The addition of the succinyl radical to sulfathiazole renders it poorly absorbable from the bowel. The free carboxyl group gives succinylsulfathiazole relatively strong acid properties and by salt formation maintains a high ionic concentration of the drug admixed with the intestinal contents. Succinylsulfathiazole, therefore, may be strongly absorbed or adsorbed by bacterial cells and may be hydrolyzed to give a high local concentration of a reactive, excited form of nascent sulfathiazole in intimate contact with the organism."

Concomitant with the reduction in the bacterial content of the stools there is a change in their physical characteristics. The stools become lighter in color, practically odorless, reduced in quantity and of a semiliquid consistency. Such

changes have been noted in some cases in which we had an opportunity to examine the intestinal contents shortly before, or in the course of, closure of a colonic stoma, when the drug had had time to exert its maximal effect

If the oral administration of succinylsulfathiazole sterilized the stools completely, one would expect to obtain favorable results without the local application of sulfathiazole in cases in which operation is performed to close a colonic stoma. Such is not the case, however. The oral administration of large doses of succinylsulfathiazole for five to seven days occasionally will reduce the number of coliform bacteria in the stools to such an extent that they cannot be found by bacteriologic examination. In the majority of cases, however, some organisms remain in the stools even after prolonged therapy with this drug. In many cases in which the drug is administered for a relatively short time, as it was in the cases in Group 1, an appreciable number of coliform bacteria must remain in the intestinal contents. The colon contains other bacteria, that is *Streptococcus faecalis*, typhoid and paratyphoid organisms and *Proteus vulgaris*, which apparently are not affected by succinylsulfathiazole. We, therefore, consider it advisable to apply sulfathiazole to the operative wound to control any infectious organisms which are not affected by succinylsulfathiazole and which inadvertently may be carried into the wound.

Recurrence of fecal drainage from the wound after closure of a colonic stoma may be due to various causes. If the colostomy spur has not been crushed adequately, the intestinal lumen may be encroached on and recurrence of fecal drainage may result. If one attempts to close the stoma too soon after it has been established, that is when the edges of the intestinal wall and the tissues about the stoma are edematous and indurated, the suture line may separate and fecal drainage recur. By far the most frequent cause of recurrence of fecal drainage from the wound following surgical closure is infection. The recurrence of fecal drainage often is preceded by obvious evidence of severe infection in the superficial layer of the wound. Subsequently, in all probability, a subfascial abscess forms which ruptures into the bowel through the suture line and externally to form a fecal fistula. That infection plays an important rôle in the formation of such fistulae is evidenced by the results of this study. In those cases in which infection was largely controlled through the use of combined succinylsulfathiazole and sulfathiazole therapy resumption of fecal drainage from the wound occurred in only two cases out of 102.\*

Reports concerning the sensitivity of patients to succinylsulfathiazole are rare. It seldom produces an untoward reaction and it is one of the most innocuous of the sulfonamide drugs. In cases in which the drug is administered as it was in the cases in Group 1, 5 to 15 Gm. of the drug probably was present in the intestine at the time of operation. Part of this is absorbed into the blood stream as sulfathiazole. In addition to this amount of succinylsulfathiazole, the tissues also contain the 5 Gm. of sulfathiazole that was applied locally. In cases

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\* In one of these cases unsuspected phlegmonous induration and edema were encountered at operation. The intestinal sutures did not hold and a fecal fistula resulted. The second failure is unexplained.

in which the patients are sensitive to sulfathiazole, one might expect a toxic reaction under these circumstances. These drugs are absorbed into the blood stream very slowly from their respective sites. In 15 of the cases in Group 1 the concentration of sulfathiazole in the blood was determined repeatedly for the first seven days after operation. In only one instance was the concentration of the drug greater than 15 mg per 100 cc of blood. In one case a value for sulfathiazole of 52 mg per 100 cc of blood was obtained 48 hours postoperatively.

A toxic reaction occurred in only two of the 50 cases in Group 1. In both of these cases the reaction occurred on the fifth day after operation. In each instance, the reaction consisted of an erythematous, urticaria-like eruption on the face, hands and lower part of the legs, edema of the affected parts, puffiness of the eyelids, severe pruritus, and increase of the temperature to 101° F. The skin lesions, pruritus and fever subsided completely by the thirteenth day after operation. The blood count was not altered in either case and no other toxic manifestations were observed. It is impossible to say whether these reactions were due to sulfathiazole or to succinylsulfathiazole.

Certain parts of the preoperative treatment previously described deserve further consideration. It would seem unwise to discontinue the administration of succinylsulfathiazole for any appreciable time before operation is performed. After the administration of the drug is discontinued, the number of bacteria in the intestine rapidly returns to its previously high level, therefore, in the cases in Group 1, the administration of this drug was continued up to four or six hours before the scheduled surgical intervention in order to obtain the maximal effect of the drug at the time of operation. If it were essential for the number of coliform bacteria to be at an absolute minimum at the time of operation, it would be necessary to alter this program. Considerable variation apparently exists in the response of different patients to succinylsulfathiazole.<sup>6</sup> Thus, in some cases it is necessary to administer the drug in large doses for from five to seven days before the maximal effect on bacterial growth in the colon is obtained. Ideally, then, one probably should culture the stools daily and defer operation until such time as the results of bacteriologic tests would indicate. At the present, however, such a procedure has not seemed advisable to us and for practical purposes the plan herein outlined, in which the drug is given for three full days and its administration continued up to within six hours of the time of operation, would appear to be satisfactory.

The combined use of succinylsulfathiazole and sulfathiazole does not eliminate the necessity of exercising good surgical judgment in selecting the time for closure of the stoma. If the spui has not been adequately crushed or is thick and edematous and surrounded by a phlegmonous induration, the results still are likely to be unsatisfactory regardless of how intensively the sulfonamide drugs are used.

Finally, the adjunctive treatment would seem to be important. Irrigations to free the bowel of impacted fecal material are always used. After the bowel is emptied satisfactorily the irrigations are discontinued so that, for at least 24

hours before operation, the intestine is put at rest and all fecal material which comes down to the stoma is well mixed with succinylsulfathiazole. Probably all of the following play important parts (1) The nonresidue diet, which reduces the bulk of the stool and in itself alters the bacterial flora favorably; (2) aspiration to empty the intestine as much as possible; and (3) administration of camphorated tincture of opium to decrease peristaltic activity during the operative procedure.

#### SUMMARY

The oral administration of succinylsulfathiazole and the local application of sulfathiazole to the operative wound have greatly improved the results which we have obtained in closure of colonic stomas. Infection of the operative wounds occurred in 84 per cent and a fecal fistula developed in 30 per cent of a series of 102 cases in which no sulfonamide drug was employed, whereas, infection of the wounds occurred in only 13 per cent and a fecal fistula occurred in only two per cent of 102 cases in which a combination of succinylsulfathiazole and sulfathiazole was administered. These improvements in the results are, in a large part, attributable to the new chemotherapeutic agent succinylsulfathiazole and they indicate in general the usefulness of this drug in the management of surgical diseases of the lower intestinal tract.

For their not inconsiderable part in working out this program and help in carrying out the many details, we wish to express our appreciation to Doctor Bargen, and his associates, in the Division of Medicine at the Mayo Clinic.

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## THE ADVANTAGES AND DISADVANTAGES OF CLOSED RESECTION OF THE COLON\*

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ON THE SURGICAL SERVICES of the Roosevelt Hospital it was maintained for many years that some form of the Mikulicz procedure was the operation of choice in resection of the colon. This attitude dated back to the work of one of our surgeons, C N Dowd,<sup>1 2</sup> whose experiences with the two-stage exteriorization method were more satisfactory and convincingly safer than with the open resections of his time. In his generation, the preparatory and post-operative measures, now familiar to all of us, were either not known or unavailable. Blood transfusion was direct, from the radial artery to the vein. The Gatch bed was a novelty. Intestinal decompression with indwelling tube and suction was unknown. Any form of primary anastomosis entailed a prohibitive mortality.

In 1939, Patterson and Webb<sup>3</sup> read before the New York Surgical Society a report of our results with the Mikulicz procedure. At that meeting the discussion and criticisms by Whipple<sup>4</sup> and MacFee<sup>4</sup> were reasonable and sound. The report was somewhat misleading, however, since it gave the impression that we had performed no closed resections. As a matter of fact, we were employing right enterocolectomy with the closed technic with increasing frequency, at first in two stages, later in one stage, with a proximal enterostomy as a vent. We had not, however, attempted, or contemplated, a primary anastomosis in the transverse, descending, or sigmoid colon for many years, although we were well aware of the favorable comment before this association, and in the literature, with respect to such a procedure.

As we continued to employ the Mikulicz-type of operation for the left half of the colon, we became increasingly conscious of certain definite objections to its use. These were (1) the necessity of multiple operations and prolonged hospitalization, (2) the distress and discomfort of abdominal fecal evacuations for a long time, (3) the questionable adequacy of removal of bowel adjacent to the growth, with the mesenteric lymph nodes, (4) the establishment of a temporary complete obstruction unless an antecedent, or complementary, cecostomy or colostomy was performed, and (5) the high incidence of complications, such as wound infection with disruption, intestinal obstruction, persistent fecal fistula, and subsequent incisional hernia. The danger of local implantation of tumor cells had been overcome by the Rankin<sup>5</sup> obstructive resection, but even this procedure, in our opinion, did not insure sufficiently wide removal to prevent local intra-abdominal recurrence of the growth.

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## CLOSED RESECTION OF COLON

Despite these objections we continued to utilize the exteriorization operation because of our firm belief that it was safer than primary resection. The reports of Whipple,<sup>6, 7</sup> MacFee,<sup>8</sup> Allen,<sup>9, 10</sup> and others, made us doubt that our attitude was entirely justifiable, whereupon we decided to employ primary resection as the opportunity arose. This report deals with our experience during the past five years.

During the years 1939 to 1943, we operated upon 110 patients with cancer of the colon, exclusive of those with tumors of the rectum and rectosigmoid. Resections were performed in 85, or 77.3 per cent, of that group. The various procedures employed and the attendant mortality are summarized in Table I.

TABLE I  
CANCER OF COLON—1939-1943

Procedure	Number	Deaths	Per Cent Mortality
Cecostomy only	6	3	50%
Enterocolostomy without resection	5	3	60%
Abdominal exploration only	2	1	50%
Peritoneal drainage only	2	2	100%
Colostomy only	8	3	37.5%
Colocolostomy without resection	2	0	0%
Balfour resection	2	1	50%
Mikulicz-type resection	18	4	22.2%
Right enterocollectomy	29	6	20.6%
Colon resection, end-to-end	36	4	11.1%
Total	110	27	24.5%

As a group, our patients represent a fair cross-section of the problems with which a busy general hospital is confronted. We receive the private patient who seeks medical attention comparatively early. We receive, as well, the ward ambulance cases brought to us in miserable condition, often with complete obstruction. There are three fatalities in our group following simple cecostomy, performed under local anesthesia, for advanced acute obstruction. Problems of this type illustrate the difficulties of comparative statistics, as Allen<sup>10</sup> has well pointed out. However, although our series is small, and though it is heterogeneous from the point of view of surgical risk, we feel that useful lessons have been learned and that significant deductions may be made.

There were five enterocolostomies of the closed type, performed simply as a side-tracking operation in the presence of extensive carcinomatous involvement which it was not feasible to resect. Three of these patients died, one of circulatory failure the day following operation, another, age 76, of bilateral pneumonia two days postoperative. The third fatality occurred 65 days after operation in a patient who had a cancer of the ascending colon with direct extension to peritoneum and other loops of bowel, with multiple fistulae, and who developed a massive retroperitoneal abscess.

One patient died following a simple abdominal exploration which revealed diffuse carcinomatosis, with ascites, the primary growth being in the cecum.

A patient, age 50, died of diffuse peritonitis following perforation of a sigmoid carcinoma. Another, age 71, had an annular carcinoma of the sigmoid which had produced a partial obstruction of long-standing. Following

perforation of a diverticulum proximal to the growth she came to us with a diffuse peritonitis, to which she succumbed. In each case only peritoneal drainage was undertaken.

There were three deaths among eight colostomies. One patient with a sigmoid growth, with liver metastases, disrupted his wound five days after a Devine colostomy had been performed. He died on the operating table, presumably of cardiac failure, while the disruption was being repaired. Another patient, age 76, went progressively downhill and died 12 days after excision of a sigmoid growth, with partial excision of the bladder. The rectum had not been removed. The colostomy and cystostomy were functioning well. The third patient, with carcinoma of the sigmoid and diffuse metastases, disrupted a left rectus wound six days after a loop-colostomy had been performed, and died ten days later.

Two resections of the Balfour-type were performed. One patient weighing 375 pounds, and presenting a sigmoid growth, with nodal and liver metastases, died on the 5th day of circulatory collapse following wound disruption.

In this series there were 18 exteriorizing procedures of the Mikulicz-type, with four fatalities. One patient, a severe cardiac, with complete obstruction from a sigmoid growth, had a preliminary cecostomy followed by the usual exteriorizing operations. Two months later she developed an acute small bowel obstruction to which she promptly succumbed, despite division of adhesions and enterostomy. A second patient, age 74, with an annular carcinoma of the sigmoid and a papillary cystadenocarcinoma of the right ovary, had a preliminary cecostomy, followed 17 days later by a first-stage Mikulicz procedure. She died two weeks later. At autopsy, the abdomen was free of infection. A third patient, age 76, upon whom exteriorization of a tumor of the hepatic flexure had been performed, died one week later of acute obstruction of the small bowel. Autopsy, at which no peritonitis was found, revealed complete obstruction "due to a normal appendix which had fallen over a loop of ileum, its tip becoming adherent to the mesentery on the other side." The fourth fatality, a woman, age 70, with a sigmoid carcinoma and metastases to the mesenteric nodes, had a preliminary cecostomy under local anesthesia. Nine days later, after a Rankin obstructive resection, she failed to rally and died in 36 hours of pulmonary edema.

Of the group of 29 enterocolectomies all but one were of the closed or so-called "aseptic" type. There were six deaths. One patient died suddenly of pulmonary embolism on the 9th day. Two others died of lobar pneumonia on the 5th and 8th days, respectively. A fourth patient, a severe cardiac, age 76, died ten days postoperatively. It was probably poor judgment on the part of the surgeon to undertake the procedure. Several members of the staff had advised against it. The remaining deaths were caused by peritonitis, one of them proven at autopsy to be due to leakage from the blind end of the ileum used in the lateral anastomosis.

In the group of resections of the left colon, with primary end-to-end anas-

tomosis, there were 36 cases. Eight were of the open type and 28 of the closed or "aseptic" type. In this entire group there were four deaths. One patient, five weeks after resection of a carcinoma of the transverse colon, developed an acute small bowel obstruction which was relieved by the division of peritoneal adhesions. He died 25 days later of carcinomatosis, 70 days after his original operation. A second patient, age 65, following resection of a carcinoma of the descending colon, developed an abscess of the left flank which was drained under local anesthesia five days later. He died eight days after resection, having developed a right lower lobar pneumonia. Since autopsy was not permitted we cannot exclude peritonitis as a possible cause of death, although his abdomen had been soft throughout. The third fatality occurred in a patient, age 71, who developed marked distension of the large bowel after resection of a sigmoid growth, without benefit of a preliminary vent. A cecostomy was performed four days after resection, but the patient died 14 days later, probably of peritonitis. The fourth death occurred two weeks after resection of the descending colon in a patient, age 63, from a combination of peritonitis with abscess formation and suppression of urine induced by sulfadiazine.

**COMMENT** The experience of the past five years has convinced us that our fear of primary resection with end-to-end anastomosis was unfounded, that the operation, in fact, is safer than the exteriorization method, and that it possesses a number of definite advantages over the latter procedure. The patient is subjected to only one major operation, his hospital stay is shorter, and he is not distressed by abdominal evacuations. Wound infections have been few, particularly since the use of alloy steel wire sutures for the abdominal wall, as advocated by Jones<sup>11</sup>. Postoperative incisional hernia has consequently become less frequent. We feel that we have been enabled to effect a more adequate removal of bowel and adjacent lymph nodes. An advantage of major importance is the feasibility of resection of low sigmoid growths just proximal to the peritoneal reflection, as well as growth in a sigmoid with a short mesentery or an obese abdominal wall. In the past, since such growths did not permit a satisfactory Mikulicz operation, patients were subjected either to inadequate removal of the tumor or to abdomino-perineal resection, with permanent colostomy.

In accepting the advantages of primary resection with anastomosis one should not overlook its limitations or certain ever-present hazards. In our opinion, a primary anastomosis of the colon does not remove the need of a preliminary, or complementary, cecostomy or transverse colostomy. There is frequently a temporary obstruction due to edema at the site of anastomosis, at times irrespective of the state of electrolyte and protein balance. A proximal vent in such instances will keep the bowel decompressed and thereby prevent ischemia and leakage at the stoma. The preoperative administration of sulfasuccidine and sulfathaladine, though useful in reducing the bacterial count in the colon, has not, in our hands, insured against postoperative distension. In enterocolectomy for tumors of the right colon we have employed

the Miller-Abbott tube with great satisfaction. Its efficacy in preventing distension is well recognized and, if introduced a day or two before operation, it facilitates the surgical procedure by diminishing the intrusion of the small intestine into the operative field.

Primary resection and anastomosis should not be attempted in the presence of an acute inflammatory reaction in the segment involved. Some proponents of the procedure have contended, somewhat dogmatically, that under those circumstances a simple transverse or Devine colostomy should be performed, with a secondary resection weeks or months later. The acceptance of a Mikulicz procedure in such cases, if it is feasible, seems to us a much more rational approach. In certain adherent growths with superimposed infection or localized perforation, preliminary fecal diversion will, undoubtedly, facilitate later resection. In such instances, however, our experience indicates that life expectancy is relatively short irrespective of the type of operation employed.

The technical features of primary colon anastomosis are too well known to justify detailed repetition. The adoption of oblique resection of the bowel ends to insure adequate blood supply, as advised by Lockhart-Mummery, the use of narrow-bladed crushing clamps, such as Arthur Allen has introduced, the employment of the Kerr basting-stitch, the use of interrupted fine silk Halsted sutures, and other similar refinements, have all added to the security of the anastomosis site. Although it is quite generally agreed that a peritonitis is much more likely to be due to gross leakage after closure, rather than to the minimal soiling during the performance of open anastomosis, we have, in general, preferred the closed or "aseptic" method, with the application of sulfanilamide about the site of suture.

With careful supervision of nutrition and hydration, so ably emphasized by Collier and Maddock, with safer anesthetics, and the rapid advances in chemotherapy, the literature on cancer of the colon discloses an ever increasing percentage of operability and resectability. As a consequence, we may expect more cured cases, but we must also anticipate a steady mortality rate as we accept problems which are technically more and more formidable and perplexing. Though we may favor one operative procedure over others, as a general rule, no one surgical approach is universally applicable and most of these situations will tax the skill and versatility of the most experienced surgeon. As David Cheever<sup>12</sup> has so excellently said: "Even were it desirable, it certainly is not possible completely to standardize the treatment of any disease. Such a multiplicity of variable factors are involved, in the patient himself, in his disease, in therapeutic measures, and in the physician who applies them, that any attempt at actual standardization is fallacious and unlikely to prepare the physician to meet the unusual and unforeseen situation when it arises. Nevertheless, a classification of the types of a disease and a knowledge based on experience of what measures have proved best to meet each typical condition are absolutely essential to prompt and effective action. Of no disease are these statements more true than of carcinoma of the colon,

and yet, in the selection of operative measures in this condition very great divergence of opinion exists among surgeons of experience as to what methods are best "

#### CONCLUSIONS

1 In a group of 110 patients, 85 resections were performed (77.3 per cent) We attribute this high rate of resectability to the increasing use of primary anastomosis

2 With primary end-to-end resection we have been able to excise a greater segment of the node-bearing mesentery

3 In our hands, the mortality rate of primary closed resection in the left colon is one-half the mortality rate of the Mikulicz-type of resection

4 It is our opinion that a vent proximal to the anastomosis is a necessary safeguard in primary resection

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DISCUSSION —DR W M FIROR, Baltimore Md The results of Doctor Dixon's studies are particularly gratifying because they confirm in a large number of patients the impressions we had gained from the study of a few patients The results are reassuring because Groups 2, 3 and 4 provide adequate controls for those patients treated with sulfasuxidine I was interested to see the standardization of dosage of this drug Doctor Everitt, in Baltimore, has treated a large number of patients with intractable cystitis due to *B coli* with sulfasuxidine and he has come to the same conclusion as Doctor Dixon concerning dosage He gives all of his patients the same amount of the drug regardless of the patient's weight Before hearing Doctor Dixon's results, I would have criticized the use of preoperative irrigations, but the fear we had that such enemata might dilute the concentration of the drug is unwarranted, and I think the advantage of ridding the bowel of gross fecal matter outweighs our hypothetical objection Similarly,

before hearing Doctor DIXON's paper I would have urged the postoperative administration of the drug in order to keep down the number of coliform organisms in the stool, but this, too, seems superfluous for the type of case under discussion. I do not think, however, that this precaution is superfluous when one has done a primary anastomosis in the colon, for in such patients the tissues have had no chance to develop a local immunity, and leakage of the suture line does not occur until nine or ten days after the operation.

Of course, sulfasuxidine is to be looked upon as an adjuvant in large bowel surgery. There are two distinct objections to its use: 1. It has little or no effect on the anaerobic organisms in the colon, and 2. The size and number of pills required is objectionable. Recently we have been using the phthalic acid derivative of sulfathiazole, known as sulfathalidine, the dosage of which is one-fourth that of sulfasuxidine. This drug seems to be just as effective as sulfasuxidine. I would be pleased to have Doctor Dixon try this new compound which is available for clinical evaluation in a series of cases similar to those he reported today.

DR ALLEN O WHIPPLE, New York. In these days of the indiscriminate use of bacteriostatic substances, locally and systemically, in abdominal surgery, with improvement in mortality rate attributed to them, it is wise to remember certain fundamental principles that have always determined the kindly healing of the sutured intestine and peritoneum. The first of these principles is the maintenance of an adequate blood supply to the zone of anastomosis by the careful preservation of the blood vessels in the mesentery supplying that zone. Second, the placing of an accurate seromuscular suture to provide an adequate apposition of peritoneum on either side of the suture line. This can be accomplished most certainly with a fine silk suture on a fine needle using a Lembert or Cushing type of stitch through the seromuscular layers. This is far more important than the clumsy and ineffective attempts at suturing the friable mucosal layer. In the so-called aseptic technics the mucosal stitch is never used, and reliance is placed solely on the seromuscular mattress sutures. Third, and most important, is to prevent tension on the suture line, with its accompanying tissue necrosis, by keeping the proximal segment of bowel empty of gas and fecal content.

In ileocectomy this is best accomplished by the Miller-Abbott tube introduced a day or two before the resection, in transverse and left-sided colectomies by a cecostomy a few days or a week before the resection.

TABLE I  
COLUMBIA-PRESBYTERIAN SURGICAL SERVICE  
*Radical Colon Operations—1933-1943 Inc*

Ileocectomies			Resections with Anastomosis						Rankin			Mikulicz		
			Left Colon			Transverse								
Year and P O	Deaths Per Cent		Cases	P O	Deaths Per Cent	Cases	P O	Deaths Per Cent	Cases	P O	Deaths Per Cent	Cases	P O	Deaths Per Cent
1933-1937														
60	10	16.6												
1938-1943														
117	11	9.4												
Total														
177	21	11.8	139	17	12.2	29	7	24.1	39	7	17.9	28	8	28.5

Doctor White, in his typically honest way, has reported the results in colon resections at the Roosevelt Hospital, and has shown that the previous convictions he and his colleagues had in favor of the Mikulicz operation were not corroborated by their later experience with one-stage resection whenever possible, provided intestinal decompression

is carried out either by intestinal intubation or preliminary cecostomy or colostomy. There are cases and conditions where the Mikulicz or preferably the Rankin procedure is indicated, but I am sure, as time goes on, the Mikulicz technic will be discarded for the very good reasons which Doctor White has enumerated and because of the unquestionably better morbidity and mortality rates he has obtained, and which our own statistics demonstrate (Tables I, II and III).

TABLE II  
COLUMBIA-PRESBYTERIAN SURGICAL SERVICE  
*Ileocectomies 1938-1943*

					With M -A Tube					Without M -A Tube				
Cases	P	O	Deaths	Per Cent	Cases	P	O	Deaths	Per Cent	Cases	P	O	Deaths	Per Cent
117		11		9.4	84		5		5.9	33		6		18.1

TABLE III  
CARCINOMA OF COLON  
*Follow-up Results*

Survived over 20 years (excluding 6 cases lost to F-U 21%)	15%
Survived over 15 years (excluding 9 cases lost to F-U 32%)	23.5%
Survived over 10 years (excluding 11 cases lost to F-U 45.6%)	38%
Survived over 5 years (excluding 15 cases lost to F-U 53.9%)	48.7%
Survived over 3 years (excluding 13 cases lost to F-U 71%)	66%

DR. THOMAS E JONES, Cleveland, Ohio As one who has never used intraperitoneal vaccine and never used any of the sulfa drugs in any of these cases previous to operation, I would like to show one slide in discussing Doctor Dixon's paper It may serve as a control group I merely want to emphasize the fact that it is very difficult to evaluate the importance of any one therapeutic agent

(Slide) This is a group of cases that was published two years ago. It involved the closure of a colonic stoma. There were 77 cases of operation for obstructive resection for carcinoma of the colon. The primary mortality was 65 per cent. There was spontaneous closure in 11, or 15 per cent. The total hospital stay, from preliminary pre-operative treatment, to the time the patient was discharged, was 28 days.

Broken down, the total hospital stay for closure of the stoma was only 8 days, as contrasted to 14 days listed by Doctor Dixon. Transient drainage in only 7 cases, or 10 per cent. Secondary closure was not necessitated once.

So, without benefit of any of the sulfa drugs, and with equal benefit of clergy, I propose this group of cases

(Slide) I This is a specimen partly opened up. On the one side we have typical duodenal and gastric mucosa, and in the opposite side normal ileal mucosa.

(Slide) II Here is another view of the specimen in which you can see the difference between the mucosa on the one half and mucosa on the other half

It seems to me that one must be conservative early in these hemorrhages. However, it also seems to me that if one has repeated hemorrhages it is well to perform an exploratory operation at least once (I do not think twice is necessary), to rule out any of these conditions which cannot be shown by physical examination or roentgenologically.

DR FRANK L MELENEY, New York I expected to have Albert Key ask me what I thought of Doctor Dixon's results, but I want to anticipate him by asking just two questions



Doctor Firor has said that he considers the other three groups as adequate controls

I would like to ask Doctor Dixon if the controls were run concurrently with the treated cases. I do not think we can accept, as adequate controls, cases done in a previous surgical era.

On the face of the figures it would seem to indicate that the sulfasuxidine was the important factor, because with sulfanilamide and sulfathiazole the results were similar to the controls, although slightly lower.

I think it has been definitely demonstrated that sulfasuxidine will diminish the coliform organisms, and possibly other organisms in the intestinal tract, probably washing out the colon just before operation was an added factor. I believe that if he should run concurrent controls, he might very well show a lower incidence of infection when the sulfasuxidine actually reduces the number of coliform organisms which are the most important pathogens in peritonitis.

I believe sulfanilamide is safer in the peritoneal cavity than sulfathiazole, because the latter is so slowly removed that it frequently produces adhesions, whereas, sulfanilamide is fairly promptly removed, and seldom causes adhesions unless used in very large amounts.

DR JOHN J. MORTON, Rochester, N. Y. I am glad that Doctor Whipple emphasizes bringing together without tension of the wound, either the colostomy or the resection. That, I think, is of the utmost importance. I wish to comment also on the use of suture material. Now, surgeons should have nerve enough to close their wounds completely with nonabsorbable material, and to omit the drains. They will have less wound infection and less sinuses during the convalescence.

The drain succeeds in trapping serum, and, as you know, it drains only a short time—it seals off. It acts as a culture medium. The same thing is true of absorbing and digesting catgut material. It acts as a perfect culture medium. If the surgeons will omit these, they will obtain better results.

When we have gross soiling we do not hesitate to use the sulfa drugs. In some cases the clamp slips, and then we make use of the sulfa drugs, otherwise we do not use them routinely. In our hands, since we have used sulfa drugs, the results have been much better. By that I mean intraperitoneal use of sulfathiazole mixtures with sulfadiazine and sulfanilamide, all three.

I think from our personal experience these drugs certainly do something intraperitoneally.

DR FREDERICK A. COLLIER, Ann Arbor, Mich. Our experience in treating cancer of the colon has been similar to that of Doctor White, that is, we have year by year performed more excisions, with primary anastomoses, and in the past three years we have carried these out by aseptic methods whenever possible. It is now only the rare case that is treated by exteriorization. We do not fear peritonitis from contamination during the operation, the peritonitis that is serious is the one secondary to the continuous infection from a leak in the anastomosis. This is always serious and is due to faulty technic.

However, if an open anastomosis is used, or if gross contamination occurs from accident during operation, or character of the lesion, one still does not fear peritonitis, but there will occur infection of the abdominal wall. The peritoneum is more resistant to infection than is the abdominal wall, particularly the panniculus.

For some years we have adopted the routine of delayed closure under these circumstances. The peritoneum and transversalis fascia are closed in one layer, and the superficial fascia closed as a second layer. Sutures are placed so as to close the panniculus and skin, the wound superficial to the fascia is packed with gauze. This is removed in 24 to 48 hours, and the sutures are pulled up and tied. This procedure has reduced the incidence of infection in the wall to a very small figure. If the aseptic type of anastomosis is used, and if there is no contamination, the abdominal wall is closed tight in the usual manner. We have tried the use of various sulfa drugs in the wall but we have given

them up as the wounds did not do as well. Likewise, we seldom use these chemicals in the peritoneal cavity. If one may become poetic, Doctor Dixon, we found that these agents in the panniculus act like an onion to the eye—they will weep, while the gauze of our pack acts like a handkerchief, it wipes the tears away. I was pleased to read an article of Dr. John Pemberton, that appeared about three months ago, in which he recounted his very favorable results with this method of delayed closure. I suggest that Doctor Dixon observe some of these cases, which he can do without much difficulty, and perhaps they will convince him that gauze is better than the sulfa chemicals in the abdominal wall.

DR. C. F. DIXON (closing). I should like to say a few words about the interesting series of cases presented by Doctors White and Whipple. At present, I am of the opinion that primary anastomosis following removal of growths from the left half of the colon, and, more especially, those of the sigmoid, is not as safe as the exteriorization type of operation, which leaves a double-barreled colonic stoma that must be closed later. I know that my colleague, Doctor Pemberton, is in accord with this statement. With chemotherapy making such great strides, perhaps it will be possible at some time to carry out a single-stage procedure on the left half of the colon, with as low a mortality rate as the two-stage procedure but, at present, I am reluctant to advocate it as a routine method. In dealing with lesions of the rectosigmoid I have carried out anterior resections in 126 consecutive cases in which continuity was reestablished and a temporary stoma was provided in the transverse colon. There were two deaths in this series—one was from peritonitis and the other from pneumonia Type III.

I feel just as Doctor Collier does about Doctor Jones' excellent results, but I still think that, finally, he will use sulfonamide drugs in such cases.

Doctor Meleney raised an important question. I agree with his statement that percentages relating to results cannot be considered to be accurate unless controls are run concurrently with a given series of cases, for instance, I did not have controls for the 102 cases of closure of a colonic stoma, which I reported here. However, all of the patients in the entire series were operated upon by me, with the help of the same assistants. I have not used sulfathalidine as Doctor Firor has suggested. I shall be interested in trying it.

May I add that I agree with Doctor Collier that Doctor Pemberton's method of closure is an excellent one. However, this presentation was not intended primarily to emphasize a method but rather to point out the apparent effect of certain sulfonamides in decreasing infection in and about the site of closure.

# LARGE MELENA OF OBSCURE ORIGIN\*

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HEMORRHAGE from the upper alimentary tract, with vomiting of blood as a prominent feature, has been much discussed in the medical literature. The passage of blood from lesions of the anal canal and lower rectum is a familiar phenomena. The chemical and microscopic search for constant small losses of blood in the stool is a standard method of clinical study. But the subject of this paper is different from all of these conditions, and in spite of not being rare, has attracted relatively little attention. The subject referred to is the sudden passage from the bowel of large quantities of blood, often sufficient to cause varying degrees of shock, and often with little to indicate the exact source or cause of the bleeding.

For a good many years the writer has encountered occasional cases of this sort and has developed an interest in them. The occurrence of nine such cases in his private practice within the last year has enlivened this interest, and led to a collection of such cases, herewith recorded, together with certain observations and opinions.

Excluded by definition from this discussion are those cases in which the cause of the bleeding is obvious, as for example following a surgical operation on the bowel, or association with a known blood dyscrasia such as hemophilia, or occurring in a known case of duodenal ulcer or of bowel tumor.

The typical history of the cases under discussion, which of course varies in detail, may be summarized as follows.

A person who believed himself to be in ordinary good health, is suddenly seized by an urgent desire to defecate, accompanied by a marked feeling of faintness. Sometimes the faintness precedes the bowel movement, sometimes it follows it. When the evacuated material is looked at, it is seen to be largely or wholly composed of blood. The blood may be fairly bright red, brownish-red, or tarry. Usually there are one or more subsequent similar evacuations, extending perhaps over two or three days. Then the process usually stops spontaneously leaving the patient pallid and weak and often badly frightened.

The handling of such cases involves two principal efforts. The treatment of the immediate condition and the discovery of the cause of the bleeding. The former objective is of course the more urgent. The writer has developed the following method of immediate treatment, which is not advanced dogmatically but has proved satisfactory in practice. Surgical attack is *not* seriously considered in the early stages of the illness. The poor condition of the patient and the unknown location and nature of the lesion are sufficient reasons for this decision. Such patients should not

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be subjected to an exploratory celiotomy that would very possibly be fruitless. The patient should be put to bed at once, with the feet elevated usually. Morphine hypodermically is probably useful. If the hemoglobin shows a reduction to or below 60 per cent, and if the systolic blood pressure falls below 90, a transfusion of whole blood is given. In most instances this may not be absolutely necessary, but it is the most effective and rapid restorative of the general condition. Giving the blood slowly, and not in larger quantities than 500 cc., has not been followed by harmful effects, except in one instance where a sharp chill and reaction occurred in spite of a very good match. One of the cases herewith recorded is reported to have died after a transfusion given elsewhere for a subsequent attack of bleeding, but whether there was any causal relation between the transfusion and the death is not known. The often expressed fear that transfusion may cause renewed bleeding has not been realized in practice. All food by mouth should be stopped, and only small amounts of water allowed. Intravenous fluids sufficient to keep water balance are administered. The inclusion of plasma in such fluids has been adopted in the past years and is believed to be helpful. In the great majority of cases the bleeding stops within 48 hours and the patient is rapidly rehabilitated from the early low level of the initial shock. However, such patients often require two to three weeks for complete restoration, and during this time look pale and are weak. Some of them lose as much as ten pounds in weight.

The diagnostic study of the case, except for such innocuous procedures as careful history taking, gentle abdominal examination, and rectal palpation, is best postponed until the up-turn in the general condition is well advanced. Then a sigmoidoscopic examination, a barium enema and gastro-intestinal roentgenologic study are in order. Blood studies to exclude thrombocytopenia, or other significant abnormalities, are also carried out.

As a result of the diagnostic efforts, the cases may be divided into three groups. In the first, which in my experience is the smallest group, a definite lesion, such as a duodenal ulcer, may be discovered that is adequate to explain the bleeding. In the second group, there may be found certain anomalies, not usually associated with gross hemorrhage, that may perhaps be regarded as responsible for the bleeding. Of these, multiple diverticulosis has occurred several times in this series of cases. The third group, the most interesting and largest, remains completely obscure. The history, the clinical study, and the various special investigations, including roentgenologic examination, reveal nothing of significance. The existence of this considerable group of cases is the conclusive reason against early operation. Operation under such conditions is a pure "shot in the dark." Of course in those instances where a lesion of distinctly surgical nature is discovered, the definitive treatment, after restorative measures, is operative removal.

The subsequent history of these patients is interesting. A considerable number of them *do not bleed again*. Others may bleed after long intervals of freedom—in one case in this series the interval was 20 years. Still

others may be subject to recurrent hemorrhages a number of months apart. As these recurrent cases may also belong in the group with no diagnosed lesion, the decision as to further treatment becomes very difficult. Should one sit helplessly by and let the grave hemorrhages continue, or submit the patient to an abdominal exploration that may prove fruitless? For experience has shown that even the most searching explorations may fail to disclose the source of the bleeding. Indeed, autopsy in the rare fatal cases has sometimes been reported as inconclusive in its findings. On the other hand, sometimes an exploration will reveal, and permit the removal of a lesion, that escaped detection in the study of the case. This possibility, and the natural disinclination to a course of merely passive waiting in the hope that nature may effect a cure, will usually lead to the decision to explore the recurrent cases, and with this attitude there can be no serious objection. Exactly when to operate, and after how much provocation in the form of repeated bleeding, must remain a matter of individual judgment.

The lesions that may be suspected or proved as the cause of the bleeding form a considerable and heterogeneous list. With no claim to completeness, the following conditions are mentioned. Tumors of various types, especially polyp and hemangiomata, less often malignant growths, gastric, duodenal, intestinal, and colonic ulcers, and ulcers in Meckel's diverticulum, diverticulosis, regional ileitis and colitis, vascular lesions, such as varicose veins, infarctions, miliary aneurysms, trauma from ingested foreign bodies, erosions from pressure of extra-intestinal lesions, such as aneurysms of large vessels, and other even rarer conditions. Among constitutional causes may be mentioned blood dyscrasias and hypertension.

The following collection of cases, briefly analyzed, will serve to point out, specifically, many of the foregoing general remarks.

#### BLEEDING WITH NO DISCOVERABLE CAUSE

**Case 1**—U M H 114740 R A N, white, male, age 11 months. No significant history. Severe rectal bleeding, bright red blood, 12 hours duration before admission. General and rectal examination negative. Barium roentgenogram enema negative. Hb 44.8 per cent. Other blood findings negative. Bleeding stopped in 24 hours. No further bleeding after two months.

**Case 2**—U M H 110740 V L, white, female, age nine years. Profuse rectal hemorrhage the day before admission. Similar episode five months earlier. Physical, rectal, proctoscopic and roentgenologic examinations negative except for a tiny polypus near the anal sphincter. Hb 69 per cent. No further bleeding for following ten months.

**Case 3**—U M H 64404-2 W G B, Jr, white, male, age 24. First admission March 12, 1938. Complained of passing large tarry stools for several days. At that time Hb 51 per cent. Physical and other examinations, including roentgenologic, were entirely negative. Patient was transfused and discharged. Readmitted with the same complaint and the same findings March 23, 1939. Third admission on January 26, 1940, same complaint and same findings. In the interval between these admissions the patient had no symptoms and seemed completely well. Blood studies and roentgenologic studies each time were negative.

On April 8, 1939, an *exploratory celiotomy* was performed, with complete inspection of the gastro-intestinal tract from the diaphragm to the rectum and palpation of the

liver and the spleen *No lesion was found* An appendicectomy was performed Convalescence was uneventful It will be noted that this operation was followed again a year later by further bleeding

**Case 4**—U M H 68057 C M H, white, male, age 59 History of rectal bleeding and dark tarry stools one week before admission No massive hemorrhage Examination showed moderate arteriosclerotic heart disease Rectal examination negative Barium enema and gastro-intestinal series negative Hb 45 per cent Given four transfusions of 300 cc each No further bleeding

**Case 5**—U M H 84879 M A, white, female, age 38 Admitted with complaint of gross hemorrhage of fresh blood six weeks earlier Had been treated conservatively elsewhere, and there had been no further bleeding Patient came into the hospital for study Physical examination, including complete roentgenologic studies, was entirely negative Hb 78 per cent No further bleeding No diagnosis

**Case 6**—U M H 105465 R P B, white, male, age 55 Admitted with complaint of large tarry stools for one week before admission Only significant note in history was an appendicectomy performed four years earlier General physical examination, rectal, and proctoscopic were all negative On this admission, January 1, 1943, complete roentgenologic studies of the gastro-intestinal tract were negative Hb 51 per cent Given two transfusions Was discharged January 13, 1943, there having been no further bleeding Patient was readmitted November 9, 1943, with another sudden onset of rectal bleeding The entire examination including complete roentgenologic studies was completely negative Hb this time dropped to 44 per cent Received two blood transfusions There has been no subsequent bleeding to date

**Case 7**—J H H A-4266 W L, colored, male, age nine years, ten months Patient was admitted January, 1938, with history of several fainting attacks in the previous three weeks, leaving him weak and pale, and followed by tarry stools There had been some vomiting associated with some of these attacks On admission his Hb was 40 per cent Examination otherwise was negative He was readmitted to the hospital in May, 1938, with epigastric pain, vomiting of food with some blood and two tarry, black stools Hb 65 per cent, which later fell to 35 per cent The patient was treated with transfusions and intravenous fluids until recovery from shock An *exploratory celiotomy* was then performed, which was negative, except for some lymphoid hyperplasia Patient was readmitted December, 1938, with a history of some recent pain in the left upper quadrant, vomiting of some blood and bloody stools Examinations, including repeated gastro-intestinal and barium enema roentgenologic studies and gastric analysis, were entirely negative Blood studies were also negative There was another recurrence in March, 1939, again, in November, 1939, at which time further examinations including sternal biopsy were negative There was still another recurrence in March, 1940, at this time, a study of possible allergies was made, which was negative A *second celiotomy* was performed Fluid blood was seen in the small bowel but no etiologic factor could be found During convalescence an esophagoscopy was done, which was negative A note, as of January, 1943, reports no further bleeding

**Case 8**—J H H 284779 W E H, white, male, age 16 Patient was admitted to the hospital, with a complaint of weakness and pallor for several weeks and large tarry stools for two days previous to admission Abdominal examination, roentgenologic studies, blood studies, gastroscopy and proctoscopy were all negative Conservative treatment No further bleeding

**Case 9**—J H H 127438 R H, white, male, age 25 Some epigastric pain of short duration five months previously, and again two months previously Relieved by vomiting Has lost 20 lbs in three months After an indiscretion in diet, the night before admission, he became suddenly nauseated and vomited Following this he grew very thirsty, and fainted There was some blood in the vomitus On admission, was found to have bloody stools, the abdomen was negative, gastro-intestinal roentgenograms

were negative Hb 42 per cent Conservative treatment No further bleeding This case may have been one of duodenal ulcer, but no lesion was demonstrated

Case 10—J H H 215216 J H R, white, male, age 26 Appendix removed at age 12 Complained of abdominal discomfort the night before admission Was nauseated, and fainted when he tried to vomit Next day passed tarry stools Abdominal examination negative Hb 65.5 per cent Roentgenologic studies showed spastic bowel, but no lesion All other examinations were negative Conservative treatment Bleeding stopped

Case 11—J H H 177634 T M, colored, male, age 36 Appendix removed five years before Sudden weakness and dizziness while at work the day before admission Nauseated but did not vomit Next day vomited some bright blood Abdomen negative Hb 42 per cent Stool positive for blood Roentgenologic studies negative Gastric analysis and proctoscopic examination negative Transfusion Conservative treatment Discharged Recurrence of bloody stools after two years and again, five months later, at which time diverticula were suspected in the ascending colon Recurrence again after six years, and again 11 years later On this last admission all examinations including roentgenologic, gastroscopic and proctoscopic were reported as negative

Case 12—J H H 130524 G D, colored, female, age 38 Has had epigastric pain and soreness at intervals during three years before admission, which would disappear spontaneously Two weeks before admission became extremely weak and tired, was notably pale, and for the first time passed large tarry stools Abdominal examination was negative Hb 50 per cent Stools negative for parasites Gastro-intestinal roentgenologic studies negative, were repeated, and again negative Gastroscopic examination negative Conservative treatment with transfusions Discharged improved, was well one year after

Case 13—J H H 74517 C McC, white, male, age 40 Mild indigestion for eight years, occasionally vomited, never any blood Five days before admission felt weak passed a large tarry stool Four days before admission, felt nauseated and fainted Abdominal examination negative Hb 48 per cent Gastro-intestinal roentgenologic studies and blood studies negative Conservative treatment Discharged improved

Case 14—J H H 177821 J B, colored, male age 43 Just before admission had fainting attack and a large hemorrhage from the rectum Abdominal examination negative Hb 57 Gm STS positive Gastro-intestinal and barium enema studies were negative Proctoscopic examination was negative Conservative treatment with transfusions Recurrence of tarry stools two years later and again, three and one-half years later, with considerable shock Recurrence again five years later, with vomiting of some blood At this time, blood studies were all negative Gastro-intestinal and barium enema studies were negative Proctoscopic examination negative *Exploratory celiotomy* negative No lesion found Two years later had had no recurrence

Case 15—J H H 235073 O T N, white male age 44 May, 1939, passed tarry stools and vomited some blood Felt quite weak Roentgenologic studies reported as negative In June, 1941, again, passed large tarry stools for two or three days Hb 76 per cent Gastro-intestinal roentgenologic studies and barium enema negative Conservative treatment Discharged improved

Case 16—J H H 53744 J J, colored, female, age 47 Increasing constipation for two years Twenty pounds weight loss in six months Ten days before admission felt faint and had to lie down, and next day passed one pint dark clotted blood from the rectum During the succeeding ten days passed blood from rectum on several occasions No pain but increasing weakness and some vomiting Abdominal examination negative Hb 29 per cent Gastro-intestinal roentgenologic studies negative Barium enema showed a constriction at the rectosigmoid Proctoscopic examination negative *Exploratory celiotomy* No lesion found Later, barium enema was repeated, and this time the constriction was reported at the splenic flexure Discharged improved

Case 17—J H H 53669 R V O, white, male, age 49 No previous symptoms Malaise and weakness all day Collapsed when he went to toilet Passed large tarry stool Abdominal examination negative Hb 70 per cent S T S positive Other examinations negative Conservative treatment No further bleeding

Case 18—J H H 73665 J S, white, female, age 51 Six attacks of abdominal pain in the epigastrium during the year before admission On day of admission awoke dizzy with severe headache Fainted on slight exertion Tarry stool Hb 40 per cent Gastric analysis negative Gastro-intestinal series and barium enema negative Conservative treatment with transfusions Discharged improved Later, had another occurrence of tarry stools

Case 19—J H H 141314 S G, white, male, age 52 Was admitted to the hospital with acute pulmonary edema While on the ward had a sudden, severe pain in the left mid abdomen with vomiting Passed large stool containing blood Abdominal and rectal examinations were negative *Exploratory celiotomy* No lesion found Discharged improved

Case 20—J H H 195992 S W E, white, female, age 52 Three years before admission patient had had a sudden attack of nausea, headache and abdominal discomfort and passed large bloody and tarry stools All examinations were said to have been negative Recurrence some months later Examinations again negative *Exploratory celiotomy*, performed elsewhere, was reported negative Since that time has had repeated intermittent episodes of tarry stools and weakness Abdominal examination negative Hb 61 per cent Gastro-intestinal roentgenologic examination negative *Exploratory celiotomy*, performed elsewhere, was reported negative Since that time has had repeated intermittent episodes of tarry stools and weakness Abdominal examination negative Hb 61 per cent Gastro-intestinal roentgenologic examination and barium enema negative, except for possibly abnormal loops in the region of the terminal ileum Operation was refused Patient discharged

Case 21—J H H 227811 G C, white, male, age 53 Sudden, severe crampy pain in the thighs and abdomen Several hours later vomited large amount of fluid Abdominal examination negative Gastric analysis negative Gastro-intestinal roentgenologic studies, at this time, were interpreted as showing dilated esophagus Conservative treatment Patient discharged improved Eight months later, patient readmitted, with large tarry stools and weakness Gastro-intestinal roentgenologic studies, at this time, were interpreted as negative Esophagoscopy negative

Case 22—J H H U-74670 G H, white, female, age 53 Since the age of 25 has had irregular attacks of indigestion with crampy pains in the lower abdomen On the day before admission, following a meal, she was nauseated, felt some tightness in the epigastrium, and then passed a large tarry stool, and fainted This was repeated again later Patient induced vomiting and brought up some dark, reddish material Abdomen very fat but negative on examination Hb 65 per cent Gastroscopic examination negative Gastro-intestinal and barium enema series were negative Conservative treatment Reported seven years later as being well during the interval

Case 23—J H H 192752 H B, white, male, age 53 Chronic constipation and indigestion About six months ago vomited some blood and passed dark stools streaked with blood Similar attacks four months ago Had lost 15 pounds in six months Shortly before admission vomited a little blood and passed large, dark stools with blood clots Abdominal examination negative Hb 35 Gm Gastro-intestinal roentgenologic studies showed some delay in passage of barium through the small bowel Barium enema was negative Esophagoscopy unsatisfactory Conservative treatments with transfusions Discharged improved

Case 24—J H H 290050 F W L, white, male, age 54 Two weeks before admission a few bright red blood streaks noted on stool Morning of admission, large tarry stool, with blood Felt weak and fainted Abdominal examination negative



Barium enema negative Proctoscopic examination negative Conservative treatment with transfusion Discharged improved No further bleeding for one year

**Case 25**—J H H 39479 L S, white, female, age 56 Past history negative Sudden faintness and desire to defecate Passed large amount of dark, red stool, which was repeated three times in 30 minutes Increasing weakness, dizziness and palpitation Several more dark stools during the following few days Abdomen negative Hb 40 per cent Gastro-intestinal and barium enema roentgenologic studies negative Conservative treatment Discharged improved

**Case 26**—J H H 135648 W J J, white, male, age 49 Past history negative Passed large tarry stool, and felt faint while at work Abdominal examination negative Gastric analysis negative Gastro-intestinal and barium roentgenologic studies negative Conservative treatment

**Case 27**—J H H 159583 J LaR, white, male, age 59 Indigestion for many years Relieved by soda Vomited several times, and on the last occasion noted some bright red blood Passed large, tarry stool the next morning Abdominal examination negative Hb 77 per cent Gastro-intestinal roentgenologic studies negative Conservative treatment

**Case 28**—J H H 230193 S H, white, female, age 64 Past history negative Sudden attack of vomiting, felt cold and clammy In later attacks of vomiting some bright red blood Passed blood per rectum several times Slight abdominal pain Abdomen negative Hb 88 per cent Gastro-intestinal studies and barium enema negative Conservative treatment

**Case 29**—J H H 180361 M W, white, female, age 66 One year of indigestion, without relation to meals On day before admission, marked dizziness and weakness, with a desire to defecate Passed large tarry stool Next day stools continued to be large and tarry and vomited some dark material Abdominal examination negative Hb 51 per cent Gastro-intestinal and barium enema roentgenologic studies negative Conservative treatment with transfusion

**Case 30**—J H H 163115 C B H, white, male, age 77 Some epigastric pain and belching at times for several months Had passed dark stools for past three weeks On day before admission felt cold and very weak, and had urgent desire to defecate Passed large tarry stools Shortly afterward vomited considerable amount of blood, with some epigastric discomfort Abdominal examination negative Hb 40 per cent Gastro-intestinal series negative Barium enema was interpreted as negative, but the cecum was not well visualized Patient had an unexplained fever of 102° F, with leukocytosis during his stay in the hospital Conservative treatment with transfusions Discharged improved

**Case 31**—J H H 27890 M K white, female, age 79 Epigastric discomfort and belching for the past year Sudden nausea and vomiting, no blood Passed large stool containing large amount of old, dark blood Patient became quite pale One or two dark stools for the next two or three days Abdomen negative Hb 45 per cent Conservative treatment with transfusions Patient left the hospital without permission Two weeks afterwards recurrence of tarry stools Patient died following a transfusion given elsewhere

#### CASES WITH POSSIBLE EXPLANATIONS

**Case 1**—U M H 90509-2 S H C, white, male, age 64 Patient has had a history of occasional epigastric pain, relieved by soda Pain usually occurs at night or when stomach is empty Gallbladder removed for gallstones two years previously Twenty-four hours prior to admission had an attack of nausea followed by the passage of four large tarry stools Abdominal examination showed hernia in the scar of the previous operation, and patient was much overweight Hb 44.8 per cent Gastro-intestinal

series and barium enema negative, except for spasm at the rectosigmoid junction Proctoscopic examination negative Conservative treatment with transfusions

In view of the history and the fact that the roentgenologic studies were handicapped by obesity, this case might be attributed to duodenal ulcer No further bleeding since discharge from the hospital Patient on ulcer treatment

**Case 2**—J H H 122580 R A P, white, male, age three years Occasional bright blood in the stools for 1 5 years Polypus removed on two occasions from the rectum Before admission passed large bright red stool Three separate roentgenologic studies of the colon failed to reveal any lesions

This case may be attributed to polyp not detected roentgenologically

**Case 3**—U M H 85859 P E R, white, female, age 12 Patient had been treated for anemia, with tarry stools, three years before admission Two days before admission passed large, tarry stool mixed with some bright red blood Abdominal examination negative Gastro-intestinal and barium roentgenologic studies negative Proctoscopic examination negative Patient continued to pass blood from the rectum in spite of repeated transfusions *Exploratory celiotomy* No lesion found except large tortuous blood vessels in the wall of the small intestine, especially the lower jejunum, and some lymphoid hyperplasia Appendix removed After operation, several roentgen-ray treatments were administered to the abdomen No further bleeding during the next year

This case may be explained on the basis of the dilated blood vessels in the intestinal wall

**Case 4**—U M H 47047 W S B, white, male, age 58 Admitted to the hospital with complaint of weakness, fainting and tarry stools during previous week Previous similar attack six months earlier Recovery and second admission for similar complaints six months later Repeated roentgenologic studies and proctoscopic studies were negative Two years later, patient admitted to hospital for severe nose bleed and hypertension (220/130) This had developed subsequent to his first admission On a third admission, another two years later, patient had a cerebrovascular accident, with a left hemiplegia Patient recovered from this, and three years later was again admitted because of the vomiting of a large amount of blood

This case may be understood as one of progressive hypertensive disease with arteriosclerosis, the first evidence of which was bleeding from the bowel

**Case 5**—J H H 237884 J D, white, male, age 66 No previous symptoms Three days before admission, faintness, nausea and five large tarry stools, with some bright red blood This was repeated for the following two days Abdomen showed slight ascites Liver two fingersbreadth below costal margin Gastro-intestinal and barium enema roentgenologic studies negative Hb 76 per cent General examination showed arteriosclerotic heart disease

This case, like the preceding one, was probably bleeding due to vascular disease

**Case 6**—U M H 109555 R S, white, female, age 17 Patient first admitted with a history negative except for three episodes of gross hemorrhage from the bowel during the preceding three months The blood was bright red Past history was negative, except for appendectomy two years previously All examinations were negative The patient was discharged Patient was readmitted four months later because of another attack of rectal bleeding At this time, there was slight tenderness in the lower

abdomen, and a presumptive diagnosis of Meckel's diverticulum, with bleeding, was made *Exploratory celiotomy*. The only abnormality found was a small indurated area in the wall of the cecum, which appeared to be where the appendix stump had been inverted. This area was excised. Microscopic examination was reported as granuloma of the cecum. There has been no bleeding since the operation.

The lesion described may have been the cause of the bleeding, but it was so small that the operating surgeon was skeptical about its importance.

**Case 7**—J H H 212683 M L, white, female, age 62. No previous symptoms. Awakened early in the morning with indigestion and sudden vomiting. The next day felt weak and dizzy, and passed large tarry stools with bright red blood. This continued for a few days before admission. Abdomen negative. Hb 40 per cent. All special examinations morning with indigestion and sudden vomiting. The next day felt weak and dizzy, and passed large tarry stools with bright red blood. This continued for a few days before admission. Abdomen negative. Hb 40 per cent. All special examinations negative, except for the barium enema roentgenologic study, which showed numerous diverticula of the descending colon and sigmoid. Conservative treatment. Discharged recovered.

This case, with several others, suggests that diverticulosis of the colon may at times be associated with good-sized hemorrhage into the bowel and no other symptoms.

**Case 8**—J H H 237865 D S H, white, male, age 47. No previous symptoms until eight months before admission, when patient had vomiting, epigastric cramps and passed several large tarry stools. Three days before admission, patient again passed a large, black stool. Abdomen negative. Hb 90 per cent. Examinations negative except for a diverticulum of the descending colon and two areas of constriction. Conservative treatment. Recovery.

This is another case of diverticulosis.

**Case 7**—J H H 149641 M H, colored, male, age 68. Alternating diarrhea and constipation for about three years. Sudden fainting attacks. Passed large stool containing clotted blood, and continued to pass tarry stools for the next two or three days. Abdomen negative, and other special examinations negative, except for barium enema studies showing diverticula of the large bowel and a filling defect at the rectosigmoid junction. *Exploratory celiotomy* negative except for diverticula. Patient discharged improved.

This is another case of proved diverticulosis.

**Case 8**—J H H 210100 R H, white, male, age 78. Some indigestion and nausea for two to three years. More frequent in past 4-5 weeks. Five days ago severe epigastric pain. Two days ago another attack of pain followed by several tarry stools and increasing weakness. Abdomen shows slight tenderness in the left epigastrium. Liver and spleen just felt. Hb 12.6 Gm falling later to 6.5 Gm. Barium enema roentgenogram shows diverticula in the transverse colon. Other examinations negative. Conservative treatment with transfusion. Patient discharged improved.

Another case of diverticulosis, with bleeding.

**Case 9**—U M H 67631-2 W F V, white, male, age 70. Three weeks before admission massive rectal hemorrhage, with faintness. Previous history negative except for hernia operation and chronic gout. All examinations were negative except that

the roentgenologic studies showed one large diverticulum in the third portion of the duodenum and extensive diverticulosis of the entire colon Conservative treatment Recovery

Another case of diverticulosis, with bleeding

Case 10—U. M. H. 71293 A. E. McB., white, male, age 60 Past history negative except for asthma Sudden massive rectal hemorrhage, with faintness, on the day of admission All examinations negative except the roentgenologic studies of the intestinal tract. These showed an herniation of the cardiac end of the stomach through the esophageal hiatus, and numerous diverticula of the sigmoid

This patient had diverticulosis of the colon and an esophageal hernia

Case 11—U. M. H. 61112 A. B. S., white, male, age 67 Past history negative except for slight rectal bleeding five years prior to admission One week prior to admission patient had some pain in the right lower quadrant of the abdomen Five days later he passed approximately a pint of blood from the rectum General examination was negative except for a systolic murmur at the apex Roentgenologic studies showed diverticulosis of the sigmoid All other examinations were negative Hb 57 per cent Bleeding stopped the next day This patient has been followed for seven years and has had no further bleeding

Another case of diverticulosis, with bleeding

Case 12—U. M. H. 113708 M. N., white, female, age 64 Past history entirely negative except for occasional constipation Profuse hemorrhage from the rectum of bright red blood four hours before admission Abdominal examination negative Hb 69 per cent Roentgenologic studies negative except for very extensive diverticulosis of the entire colon Conservative treatment, with transfusions No further bleeding

Another case of diverticulosis

Case 13—J. H. H. 263150 K. S., white, male, age 22 A number of large bloody stools a few hours before admission Hb 83 per cent Proctoscopic examination negative Patient had had appendix removed, with drainage, seven years before Gastro-intestinal series showed irregularities in the lower ileum and delay in passage Conservative treatment, with recovery

Considered possibly regional ileitis

Case 14—J. H. H. 162035 L. O. H., white, male, age 30 Two previous episodes of tarry stools and vomiting, eleven and nine years previously No lesion demonstrated at any time Admitted for tarry stools and weakness Abdomen negative Hb 50 per cent Roentgenologic studies negative Gastroscopy negative A second gastro-intestinal roentgenologic examination was interpreted as showing persistent deformity of the duodenal bulb, and the questionable diagnosis of ulcer was made Conservative treatment Recurrence three years later of tarry stools This time, with lower abdominal cramps On this occasion, roentgenologic studies were again negative

This case may be considered one of possible duodenal ulcer

Case 15—J. H. H. 210538 G. A., white, male, age 47 Patient had been a heavy drinker Five years previously had vomiting episode, and brought up some blood Three days before admission had sudden weakness and dizziness while at work, and passed tarry stools for the next three days No pain, nausea or vomiting Abdomen negative.

Hb 68 per cent Gastro-intestinal series and proctoscopic studies were negative Liver function tests showed evidence of hepatic damage

Case considered possibly one of cirrhosis of the liver

**Case 16**—J H H 207504 C H, white, male, age 52 Ten years before admission had severe hemorrhage from the rectum, which was attributed to a duodenal ulcer for which an operation was performed One month before admission, again, had severe hemorrhage from rectum Abdomen negative Hb 77 per cent Roentgenologic studies showed a diverticulum in the second portion of the duodenum Conservative treatment No operation

Possibly an instance of bleeding duodenal diverticulum

**Case 17**—J H H 224977 A R, white, male, age 54 Complaint tarry stools, diarrhea, weakness Abdomen obese Negative on examination Hb 41 per cent Gastro-intestinal series showed a diverticulum in the esophagus Conservative treatment, with transfusion Discharging fluid

Possible bleeding due to diverticulum of the esophagus

**Case 18**—J H H 160683 J M B, white, female, age 56 Increasing indigestion for six months Nausea and vomiting for seven days before admission Some blood in the vomitus at times Stools were very black Abdomen negative Hb 44 per cent Hypertension Other examinations all negative Conservative treatment Two years later recurrence, and five years later a second recurrence

This may have been a case of alimentary hemorrhage from hypertension

**Case 19**—J H H 227522 J P M, white, female, age 66 Had had several abdominal operations previously Had had hypertension for many years Just before admission had nausea and vomiting, and passed a very large and bloody stool, followed by fainting Abdomen negative Hb 70 per cent B P on admission 180/100 All other examinations negative Conservative treatment Discharged improved

This, also, may be a case of bleeding from hypertension

**Case 20**—E H H (personal friend), white, male, age 64 Attack of fainting followed by passage of large tarry stool, in 1913 Studies at this time were inconclusive Recurrence of similar attack 20 years later, in 1933 Patient quite well in the interval Following the second attack roentgenologic studies were interpreted as showing some distortion of the duodenal bulb and probable diagnosis of duodenal ulcer was made

Possibly an instance of bleeding from a duodenal ulcer

#### GROUP OF CASES WITH PROVED CAUSES

**Case 1**—C H H 35521 J B, white, male, age 32 Two days before admission had some abdominal cramps and gurgles, and early the next morning passed a large amount of blood per rectum No other symptoms Barium enema showed filling defect in the descending colon Resection and anastomosis with removal of a malignant growth was performed Recovery

**Case 2**—U M H 105168-2 R B D, white, male, age 71 On previous admission patient had passed a large amount of blood and general examination, including roentgenologic studies, had been negative Recurrence of symptoms one year later, at which time roentgenograms showed carcinoma of the cardiac end of the stomach The films were interpreted as indicating an apparently inoperable condition and, in any event, the patient refused surgery

## MELENA OF OBSCURE ORIGIN

Case 3—J H H 295336 J F H, white, male, age 61 History of bloody stools three months before admission Some vomiting of blood three years before that While in hospital he passed large tarry stool Died Autopsy showed cirrhosis of the liver and thrombosis of the portal vein

Case 4—J H H 232449 W M, white, male, age 57 Strong history of alcoholism Admitted to the hospital for vomiting and bloody stools Hb 44 per cent Died Autopsy showed nodular cirrhosis of the liver, enlargement of the spleen and esophageal varices

Case 5—J H H 112680 L W, colored, female, age 30 Sore throat 25 weeks before admission followed by fever and passing of blood per rectum Patient died in the hospital and, at autopsy, was found to have a subacute gastro-enteritis, organism undetermined, with massive hemorrhage into the ileum and colon

Cases 6, 7 and 8—J H H 127538, J H H 107352, and J H H 135006 These three cases all presented blood in the stool as a chief symptom, and were all diagnosed gastric ulcer on roentgenologic or other evidence

Cases 9, 10 and 11—J H H 152677, J H H 162159, and J H H 272856 These three cases all presented blood in the stool as an important symptom, and all were proved to have carcinoma of the stomach

Case 12—J H H A-6901 C E G, colored, male, age 14 months Vomiting of blood and blood-stained stools At operation, based on roentgenologic evidence, a duodenal cyst was found and removed Recovery

Case 13—J H H 195622 C F F, white, male, age 43 Bleeding into the bowel chief symptoms Roentgenologic diagnosis of diverticulum of the duodenum Operation—excision of diverticulum Discharged well

Case 14—J H H 260056 M H, white, male, age 21 Two years before admission profuse bleeding from rectum Gastro-intestinal series negative Recurrence of bleeding at time of admission Several large, dark bloody stools Some pain to the left of the umbilicus Exploratory celiotomy Regional ileitis Resection and anastomosis Recovery

Case 15—J H H 200330 N C, colored, female, age 37 Nausea and vomiting Passage of large amount of bright red blood per rectum Hb 62 per cent Conservative treatment Recurrence five months later Exploratory celiotomy Regional ileitis Resection and recovery

Case 16—J H H 152963 W S, white, male, age 38 Tarry stools for eight days Hb 57 per cent Gastro-intestinal series showed a constriction at the pylorus Exploratory celiotomy Stomach and pylorus normal Meckel's diverticulum found and resected Recovery

Case 17—J H H 286391 G W, white, male, age 22 Injection of some sclerosing fluid by physician two months before admission Nine days before admission bright red blood in large quantities in stool continuing since that time Examinations, including proctoscopic, were negative Exploratory celiotomy was negative Profuse bleeding after operation, at which time an artery in the rectal wall was discovered to be spurting Controlled through the proctoscope

Case 18—J H H 181633 M P, white, male, age 72 Massive hemorrhage from bowel Lymphoid leukemia

Case 19—J H H 180084 H S P, white, male, age 26 Massive hemorrhage into the bowel Myeloid leukemia

Case 20—J H H 4486 M L, white, male, age 41 Large intestinal hemorrhage Hemophilia

Case 21—J H H 252723 S K W, white, male, age 40 No previous symptoms Large bloody stools for the past two months Admission because of sudden abdominal cramps, with massive bloody stools Conservative treatment Patient bled to death in spite of transfusions Autopsy showed carcinoma at the splenic flexure of the colon

The cases herewith recorded are too few and too heterogeneous for statistical study, but certain facts are evident. The patients were of all ages, of both sexes, and included both Negroes and whites. The patients with proved causes of bleeding present a variety of lesions, some of which may have been present but undiscovered in some of the unexplained cases. The fairly numerous cases of diverticulosis of the colon, associated with bleeding, may indicate that hemorrhage into the bowel is a more common occurrence in this condition than is generally believed. Similar bleeding must be recognized as an occasional symptom of the latter conditions reported among the proved cases. The outstanding observation, however, is the quite considerable group of patients with large melena in whom careful and extensive study failed to reveal any explanation of the source or cause of the hemorrhage.

#### SUMMARY AND CONCLUSIONS

(1) Report is made of a collection of cases in which the presenting symptom was large hemorrhage, passed per rectum, of obscure origin.

(2) The opinion is expressed that restorative treatment followed by careful study is the proper immediate treatment, and that early operation should not be advised.

(3) These cases may be divided into three groups: (a) Those in which study reveals the definite cause of the bleeding, (b) those in which a lesion is discovered that perhaps accounts for the bleeding, and (c) those where exhaustive search fails to show any explanation.

(4) The subsequent history of these patients with no detectable lesion may be free from any further bleeding, or subsequent hemorrhages may occur at varying intervals.

(5) Surgical treatment should be carried out when a lesion of the type amenable to operation is definitely diagnosed after adequate study. Where recurrent bleeding is associated with a lesion that *might* be responsible, and this lesion is suitable for surgical intervention, operation should be advised. In the cases that remain completely unexplained, operation is only a resort of desperation in the face of repeated grave hemorrhages. Such an operation may still fail to discover or relieve the trouble.

The writer expresses his thanks and obligation to Dr. Frank Inue for his help in collecting the data on the cases from the Johns Hopkins Hospital, and to Dr. Ray Curtis, for similar kindly services at the Union Memorial Hospital.

**DISCUSSION**—DR. DAMON B. PFEIFFER, Philadelphia: This is a strong clinical paper and valuable compilation of cases. Doubtless, nearly all of us, being clinical surgeons, have encountered cases similar to those which are related in detail by Doctor Stone.

It is difficult for any man, however, to accumulate a great deal of personal experience, because such cases come along sporadically and in small numbers.

McBurney once said, "Lord deliver me from man of one case." However, many cases individually collected and analyzed are in reality a clinical research. I would like to add, very briefly, a few cases which have come under my own observation.

About ten years ago, a man, age 57, was sent to me at the Abington Hospital, after a very severe, exsanguinating gastric hemorrhage. He had had typical ulcer symptoms

30 years before, associated with frequent severe hemorrhages and melena, and after five years he was sent to the late John B. Deaver, who explored him in the German Hospital, now the Lankenau. The roentgenograms had been negative. Everything else was negative, but Doctor Deaver was convinced from the history of this man that he had an ulcer.

He found nothing by palpation and general exploration, but being sure that there was an ulcer he made a gastrotomy and examined every bit of that man's gastric mucosa. Finding nothing, he closed him up. The duodenum seemed normal.

A year later the man had the same kind of hemorrhage. Again he was brought to the hospital, this time being wary. He was examined medically, nothing was found. Doctor Deaver declined to do anything more, and a tentative diagnosis of purpura haemorrhagica intestinalis, was made.

He continued at intervals of a year or a year and a half to have the same kind of hemorrhages. About the time he got built up he would be bled out again. He would get well in the meantime.

With each hemorrhage he would have symptoms somewhat indicative of ulcer. Finally, after he had had about a 20-year siege of this thing, he was brought to me. I advised operation because he was exsanguinated and I felt sure from his history that he must have an ulcer. He refused to have the operation, and left. Eleven months later he had another such hemorrhage. This time he gave in and I explored him.

I found no evidence of an ulcer directly, but where the duodenum approached the liver there was obviously an area of inflammation and adhesions. I decided to explore his duodenum. I made a duodenotomy, and there, sitting on the head of the pancreas, burrowing into it to some extent, but not enough to make a crater that you could feel with your finger, was a huge ulcer the size of a quarter, and in the bed of it was a plainly visible artery running across it. I destroyed the artery with the actual cautery, and finished the operation as a Finney pyloroplasty. That man in ten years has not bled nor had any symptoms of ulcer.

Let me digress for a moment and mention the control of hemorrhage in such a case. (Demonstration) I have operated upon a number of such cases. Say this is the duodenum, and here is the pancreas. We find an ulcer here with an artery running across it, or perhaps one or two openings—just a little thread of artery in between. What are you going to do about it? Are you going to tie it—are you going to lift the duodenum and tie the gastroduodenal artery here, which is an operation of some magnitude?

This experience with the cautery led me to believe that if you could cauterize an artery in such a way that it could be plugged back of the bed of the ulcer, in other words, so that gastric juices could not digest away the clot, it would be more successful than simply to tie it or to undertake the larger operation.

It occurred to me on one such occasion to bend a probe, just an ordinary little probe, the bend of which would fit into the vessel, put it in the vessel, attach the electrode to it and burn it all the way back beyond the wall of the vessel.

In one such case I was interested to find that not only was there active hemorrhage from the proximal artery, but also from the distal opening. There was enough blood coming from the distal opening to bleed profusely, which is one argument against the operation which only ties the proximal artery.

Now, encouraged by that experience, a few years later I had a man with typical symptoms like the above, four hemorrhages over a span of 11 years, and negative roentgenograms.

I explored his duodenum and found nothing. I finished his pyloroplasty, thinking he might have had hyperacidity and erosions. He bled again in a year.

Another case was a man who had been perfectly well for over 40 years, admitted with a massive hemorrhage, both from stomach and bowel. He was semicomatose on



admission. He could never be gotten into condition for operation, although he had by drop 3,350 cc of blood within 24 hours. At autopsy he had a small mucous erosion into an esophageal vein although there was no evidence of cirrhosis or of splenomegaly. No exploration ever could have succeeded in finding that lesion.

Another case was that of a woman with massive hemorrhages from the bowel. I examined her with a speculum, and there was a little spurt from a pinpoint hole in a vessel, and no surrounding inflammation. If it had not been actively bleeding I never would have found it. That would have been another case of "hemorrhage of unknown origin."

Another case, very recently, was that of a man who came in with very severe hemorrhage. He vomited some blood, but most of it passed from the rectum. He rallied from this and I went on a vacation. My associate explored him on the basis of a report from the roentgenologist that there was a suspicious lesion in his sigmoid. Nothing could be found, another "unknown origin" case.

I have had the same experience that Doctor Stone mentioned, that of bleeding in diverticulosis. I was once skeptical of it, but the coincidence is too great. I have thought of a reason which may or may not be right.

A diverticulum is a sort of "blow-out" at the point where a vessel penetrates the outer wall of the colon. Usually this goes into an epiploic appendage. Those of you who have cut off an appendage without first clamping the base will remember what a sharp little hemorrhage occurs. The diverticulum and artery are side by side in the wall, and it is easy to understand that the vessel may be eroded by a combination of pressure and infection. Bleeding will then occur into the sigmoid, and on exploration there will be no external evidence of the site.

I think Doctor Stone has rendered a useful service in collecting these cases and making us think about them. With a possible occasional exception, I agree with him entirely that if you have not the strongest clinical evidence as to what the lesion is, in the absence of any objective evidence, such as demonstrated roentgenologically, you had better let them alone.

DR THOMAS E JONES, Cleveland, Ohio. I would like to report a case, very briefly, of a young girl, five years of age, who had had repeated massive hemorrhages since the age of seven months. She came to the Clinic about a year ago, and all examinations were negative, as they are in most of these cases. Gastro-intestinal roentgenograms were negative.

The patient never had pain. Naturally, after four years of this performance it was not a very hard job to sell her parents on an exploratory operation. This was done because I felt that perhaps she might have a Meckel's diverticulum, because in the past 15 years I have had three occasions where this was the cause of massive hemorrhage.

(Slide) This is a specimen that was removed. About six or eight feet from the ileocecal valve we encountered what appeared to be a reduplication of the small intestine. This was resected and a side-to-side anastomosis made, and the patient was dismissed from the hospital on the eighth postoperative day. This is the longest time the patient has been free from hemorrhage since she was seven months of age, therefore, we are probably right in assuming that this was the cause of the bleeding.

DR ALTON OCHSNER, New Orleans, La. There are two causes of obscure bleeding from the gastro-intestinal tract that I think should be emphasized. One is cholecystitis, which may produce the typical "red stomach", the other, which has recently come to my attention, is the hemorrhage tendency resulting from the administration of large amounts of aspirin.

I recently learned from Dr Alberto Navarro, of Panama, of a patient who had recurrent massive hemorrhages from the gastro-intestinal tract. This patient had taken aspirin over a long period because of a migraine and, since it has been shown recently

that aspirin will produce an hypoprothrombinemia, it is likely that the bleeding in this case was due to this cause. Since administration of vitamin K relieved the patient this conclusion seems likely.

So it seems to me in patients in whom there is massive hemorrhage, and in whom we cannot find a cause for it, one might think of the possibility of the lowly therapeutic agent, aspirin, which is taken so readily by patients.

DR FREDERICK CHRISTOPHER, Winnetka, Ill. I want to present, very briefly, the case of a woman, age 26, who had repeated large hemorrhages from the rectum. Her hemoglobin fell to 26 per cent, and the red blood count was 1,400,000.

Upon exploration an hemangioma was found to the ileum. It was readily identified by the bright red color, and originated in the antimesenteric border, and came up both sides.

(Slide) This is a section taken through the bleeding point. After resection the patient made complete recovery.

DR PHILEMON E. TRUESDALE, Fall River, Mass. From what Doctor Stone has said, it can reasonably be presumed that all of the known causes of hemorrhage from the gastro-intestinal tract have been considered, though not mentioned. There is one which has not been presented here that I think is worthy of your attention, because it is far more common than is generally supposed. In fact, in relating the obscure causes of hemorrhage in the gastro-intestinal tract among elderly people—particularly women—that from esophageal hiatus hernia is probably the most common.

Many of these patients have passed the meridian of life, and a fairly large percentage of them is found to be anemic. If blood loss is not suspected, and the stools are not examined for occult blood, this source of hemorrhage will be overlooked. Unless this source is revealed, the hernia will remain untreated, and the cause of hemorrhage will inevitably continue, for if the presence of blood in the stools is not found before an abdominal operation is undertaken, it will not be discovered during the operation. The hemorrhage is due to abrasion or erosion, and originates from varices at the cardiac end of the stomach or from the base of an actual ulcer, both of which will be relieved by the operation for the cure of the hiatus hernia.

DR HARVEY B. STONE (closing). I want to thank the various discussers. I might say in the published form of the paper the various conditions found will be recorded in different case reports.

I want to add that you may be interested to know that among them is a spurting vessel in the rectum such as Doctor Pfeiffer recorded and two cases of diaphragmatic hernia, such as Doctor Truesdale referred to, but I think Doctor Ochsner has introduced one we did not have—the changing in the blood coagulation by the use of aspirin.

I realize that a paper such as this is apt to give rise to an experience-meeting type of comment, but I think we owe a debt to Doctor Jones for clearly pointing out that there does come a time in these cases of persistent recurring hemorrhage when you really must explore them, and when that time comes, as I said in the original talk, I think it depends upon the individual judgment of the doctor and upon the particular circumstances of the case.

# INFLAMMATORY STRICTURE OF THE RECTUM\*

AN ANALYSIS OF ONE HUNDRED AND NINETY-TWO CASES, INCLUDING  
THIRTY-FIVE TREATED BY RECTOSIGMOID RESECTION

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THE TREATMENT of inflammatory rectal stricture has long been unsatisfactory. The causal relationship of lymphopathia venereum to rectal stricture is now generally conceded,<sup>1, 2, 3, 4</sup> but there is no such unanimity of opinion regarding treatment. There are many reasons for this difference of opinion. First, the strictures vary from simple fibrous narrowings causing no symptoms to extensive lesions involving the rectum and colon with partial or complete obstruction. Second, the presence of ulcerations, sinuses and fistulae may complicate the problem. Finally, the degree of cooperation of the patient will determine management. Measures involving repeated clinic visits, prolonged administration of drugs or observance of careful hygiene are generally not employed successfully in such patients as form the bulk of our clinic practice.

The various modes of attack on inflammatory rectal stricture may be grouped conveniently under four headings: (1) Drugs and antigens, (2) irradiation, (3) dilatation, and (4) surgery. Brief reference to a few publications will indicate the experience of other authors with these methods.

*Drugs and Antigens*—Of the many drugs which have been employed in the treatment of lymphopathia venereum the sulfonamide compounds<sup>5, 6</sup> are most noteworthy. Antigens of considerable potency have recently been developed. These agents either alone or in combination have been used successfully in the inguinal or early anorectal forms of the disease and in the later active inflammatory phases. The stricture itself, however, has been affected only indirectly through control of the associated inflammation.

*Irradiation*—Reports are contradictory concerning roentgenotherapy in lymphopathia venereum even in the inguinal and early anorectal forms of the disease. After the formation of fibrous stricture it is reported to be of no benefit.<sup>7</sup> Transitory relief by short wave diathermy<sup>8, 9</sup> has been attributed to the dilating effect of the instrument inserted into the rectum.

*Dilatation*—The apparently simple and direct approach by dilatation has been widely employed both alone and in conjunction with drugs and surgery. Dilatation alone is not conspicuously successful,<sup>10</sup> and is not without danger. Warthen advocated a sigmoid colostomy with simultaneous obliteration of the cul-de-sac in order to obviate the danger of perforation during dilatation of the stricture.<sup>11</sup> He reported ten cases in which the stricture seemed to be relaxing.

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*Surgery*—Surgical efforts have been directed toward diversion of the fecal stream by colostomy, plastic procedures on the strictured area and radical resection of the infected rectosigmoid. Colostomy has usually been employed at an advanced stage, with no constant success in arresting the progress of the disease. Ingenious operations designed to enlarge the caliber of the stricture by "tunnel" grafts,<sup>12</sup> and other procedures, have not been widely employed.

Perineal resection of the rectosigmoid following colostomy was successfully carried out by Barber and Murphy,<sup>13</sup> Edwards and Kindell,<sup>14</sup> and by Bacon.<sup>15</sup> Two of these series included instances of protracted perineal infection. In 1922, Hartmann<sup>16</sup> reported two abdomino-perineal resections with one successful result and one operative death. In discussing this type of treatment, subsequent authors generally decry such an extensive operation. Morris<sup>17</sup> in 1940 reported a single successful abdomino-perineal resection for inflammatory stricture of the rectum.

#### CLINICAL MATERIAL

We have analyzed the records of 192 cases of inflammatory rectal stricture treated at the Cincinnati General Hospital during the past 25 years. All presented the clinical picture now recognized as stricture due to lymphopathia venereum. Eighty-six per cent of 105 tested cases gave positive reactions to lymphopathia venereum antigen. Whenever microscopic examination of tissue from the stricture was carried out, the picture was that of nonspecific inflammation.

A brief case summary will be illustrative.

**Case Report**—G. J., colored, female, age 37, was treated for severe proctitis during a period of seven months in 1929. At the same time she underwent hemorrhoidectomy and fistulectomy. In 1937, during hospitalization for acute pelvic cellulitis, she gave a story of progressively increasing constipation, diminution in the caliber of her stools, rectal and vaginal discharge, and intermittent slight rectal bleeding. Examination showed small granulomatous masses about the vulva with a rectovaginal fistula. Five centimeters above the anal margin there was a dense fibrous stricture which would not admit the finger tip. Kahn and Frei tests were positive. Biopsy of the stricture showed chronic inflammation. In 1939, she was treated conservatively for an episode of low intestinal obstruction. Following a second episode in 1940 a two-stage abdomino-perineal resection, by the Lahey technic, was carried out with marked improvement in her general health during the ensuing three years.

This history is characteristic of the resected cases in our series.

It should be emphasized, at the outset, that we are considering only that phase of the disease after the formation of fibrous stricture. While many authors report encouraging results in treating the early stages of the infection, results in treatment of fibrous stricture are less satisfactory.

Our cases have been divided into two groups, depending on the severity of symptoms. We have classified as "mild" those patients who have no fistulae or sinuses and whose loss of weight is below 20 pounds. We have

classified as "severe" those patients with at least one fistula or sinus or with loss of weight of at least 20 pounds. While admittedly arbitrary, this classification gives an objective basis for analysis.

Our material is derived from a general hospital in which 37 per cent of the patients are colored. In this study, however, 85 per cent of the patients were colored. As in most reported series, females predominate in a proportion of nearly seven to one. The average age when first seen was 34 years with extremes of 19 and 65. A positive serologic test for syphilis was obtained in 32 per cent. Another 15 per cent gave a history strongly suggestive of this disease.

Results have been recorded as "good," "fair" and "poor." Those who have maintained a gain in weight, who are without discharge from the perineum or colostomy, and who are free from subjective difficulty with the rectum or colostomy are considered "good." Those who maintain their weight but continue to have symptoms, such as purulent or bloody discharge, abdominal cramps or difficulty with the colostomy, are considered "fair." As "poor" results, are classified those whose symptoms are unrelieved or aggravated.

Treatment consisted of dilatation, sulfonamide therapy, roentgenotherapy and surgery. In many cases different methods of treatment were successively employed before symptoms were finally relieved. Repeated disappointment with conservative management led to increasingly frequent use of radical resection. The first perineal resections were performed by Dr. Mont R. Reid and Dr. B. N. Carter, and later radical abdomino-perineal resection was carried out at their suggestion. An attempt has been made to evaluate the independent rôle of each method in the attainment of the final result.

#### DILATATIONS

In this series 108 patients were treated by dilatation. The usual program embraced one or more dilatations under anesthesia in the hospital, with subsequent treatments in the dispensary. Eighty-two patients were subjected to 156 dilatations under anesthesia, the number of treatments varying from one to seven. There is information adequate for analysis in 77 cases, of which 32 were "mild" and 45 were "severe" (Chart 1).

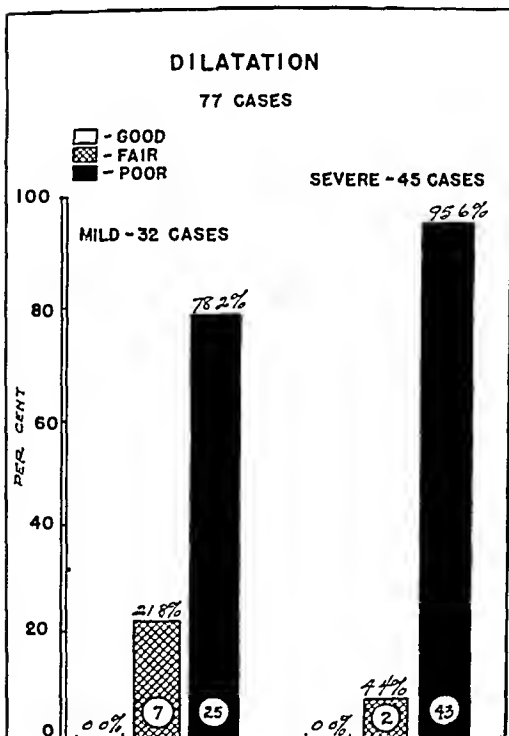


CHART 1—Results of dilatation

Of the former, seven (21.8 per cent) were "fair" results and 25 (78.2 per cent) were "poor." In the "severe" group two (4.4 per cent) were "fair" and 43 (95.6 per cent) were "poor." No "good" results were obtained by dilatation. Regardless of the trifling character of the symptoms, results are not classified as "good" unless there was definite improvement.

Four patients died of peritonitis in eight hours to ten days. Two died with a syndrome resembling shock within eight hours after dilatation under anesthesia. In one of these, autopsy showed acute gangrenous proctitis. One patient died of infection two months after dilatation. As a direct result of the disease 11 others died at periods up to 13 years after dilatation.

The average follow-up period in this group was 4.2 years. If those who died in the hospital as a result of dilatation are excluded, the average is 4.6 years, with extremes of one month and 23 years.

### SULFONAMIDE THERAPY

Our small experience with sulfonamides supports the common opinion that these agents inhibit the primary process and the secondary infection. We have not used sodium sulfanilate and sodium sulfanilyl sulfanilate, but our use of sulfanilamide, sulfathiazole and sulfadiazine has resulted in no dramatic improvement in these dense fibrous strictures. The average treatment period, however, has been insufficient to allow a fair evaluation of the drugs' effectiveness.

### ROENTGENOTHERAPY

Among seven patients treated by roentgen irradiation there were two "good" results, both of whom had colostomies before irradiation. Three of the remaining five cases had colostomy and irradiation with little benefit.

### COLOSTOMY WITHOUT RESECTION

This method was used in 34 patients, in 82 per cent of whom the disease was "severe." In contrast, the process was considered "severe" in 69 per cent of cases subjected to resection, while only 58 per cent of those treated by dilatation were so classified.

There were six "mild" cases (Chart 2) with results equally divided between "fair" and "poor."

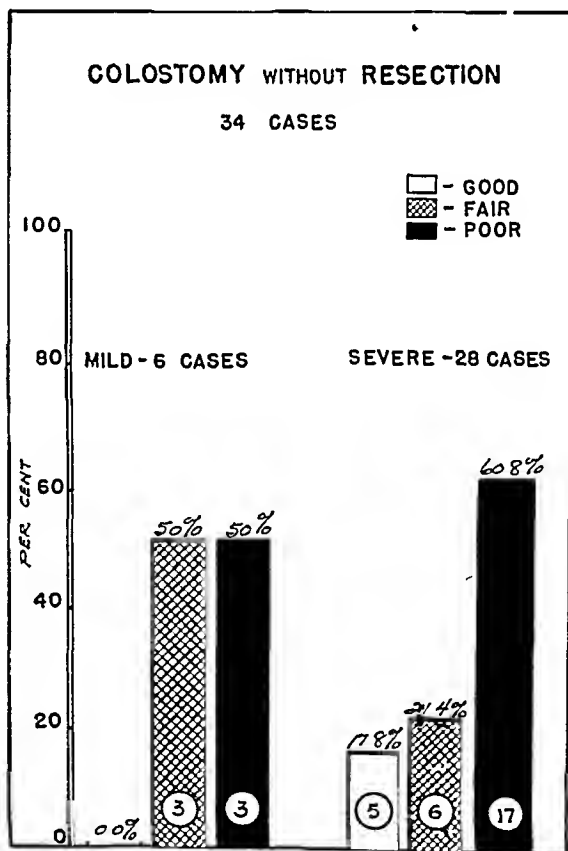


CHART 2—Results of colostomy

Death due to postoperative complications accounted for two of the "poor" results

Among 28 "severe" cases there were five (17.8 per cent) "good" results, of whom two had concomitant roentgenotherapy and one sulfanilamide. Six (21.4 per cent) were classified as "fair," irradiation being used in two. Of 17 (60.8 per cent) "poor" results, two died of postoperative complications and two developed carcinoma several years after operation.

In summary, 15 per cent of this series obtained "good" results after colostomy, while an additional 26 per cent were improved. The average follow-up period excluding those who died in the hospital was three years and nine months, with extremes of six months and ten years.

#### RADICAL RESECTION

Our experience with radical resection of the rectosigmoid for lymphopathia venereum embraces 35 cases. The average follow-up period was two years and seven months, with extremes of one month and ten years. In three, the follow-up was inadequate so that conclusions are based on 32 cases (Chart 3). Perineal resection was the procedure originally employed, but

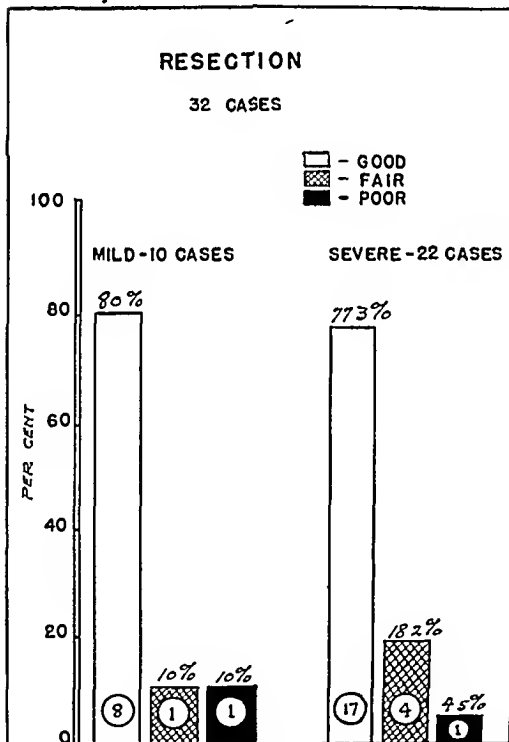


CHART 3—Results of resection

difficulties, which will be discussed later, led to adoption of the combined abdomino-perineal operation. Ten cases were of the "mild" variety. Eight of these (80 per cent) made good recoveries. One, a "fair" result, had a preliminary loop-colostomy two months before a combined abdomino-perineal resection. Though his general condition improved greatly, he continued to have bloody discharge from the blind loop distal to the colostomy. The one "poor" result had a loop-colostomy followed two years later by a perineal resection. He developed a series of perineal abscesses. The relationship of persistent perineal infection to incomplete resection of the diseased recto-sigmoid is significant.

Twenty-two cases were classified as "severe." The results of resection in seventeen (77.3 per cent) were "good." "Fair" results were obtained in four (18.2 per cent), of whom two had slight prolapse of the colostomy, one had dyspareunia and symptoms suggesting bowel obstruction, while the fourth had persistent mild diarrhea. The single "poor" result in this group had a perineal resection with persistent perineal drainage 27 months later.

There was uniformly rapid improvement in health and weight among the 25 patients considered "good" results and the five classified as "fair." In all these instances the perineal wound healed completely.

The series includes 23 combined abdomino-perineal resections in one or two stages and nine perineal resections (Chart 4). In the former group are 20 "good" and three "fair" results, while in the latter there are five "good," two "fair," and two "poor" results. We believe that the blind loop of rectosigmoid distal to the colostomy in perineal resections accounts for "poor" results in this group. Such a loop may harbor active infection leading to an unhealed perineal wound or to persistent discharge from the colostomy. Resection of the blind loop in one patient gave complete symptomatic relief.

Occasionally the disease may be found above the sigmoid. In three instances it was necessary to resect the entire left side of the colon together with the rectosigmoid. This was done once as part of the primary procedure, and twice because of granulomatous stricture developing in the sigmoid colostomy. We have not seen involvement of the right side of the colon.

In this series of 35 resections there were no operative deaths. We wish to emphasize, however, that this is a procedure of considerable magnitude, to be undertaken only after conservative methods fail.

**DISCUSSION**—A review of the preceding data affords no positive basis for choice of a single therapeutic method in all cases of inflammatory rectal stricture. Treatment in every case must be governed by the stage of the disease, the degree of cooperation of the patient and the response to conservative therapy. With asymptomatic stricture, insistence on careful hygiene and regulation of the bowels may be sufficient. Patients have been followed for as long as 20 years in this series without appreciable progression of symptoms.

With strictures showing evidence of inflammatory activity or intestinal obstruction, more active treatment is necessary. This may consist of sulfonamides, with which good results have been reported both in the early stages of the disease and in secondary infections. While our experience has been

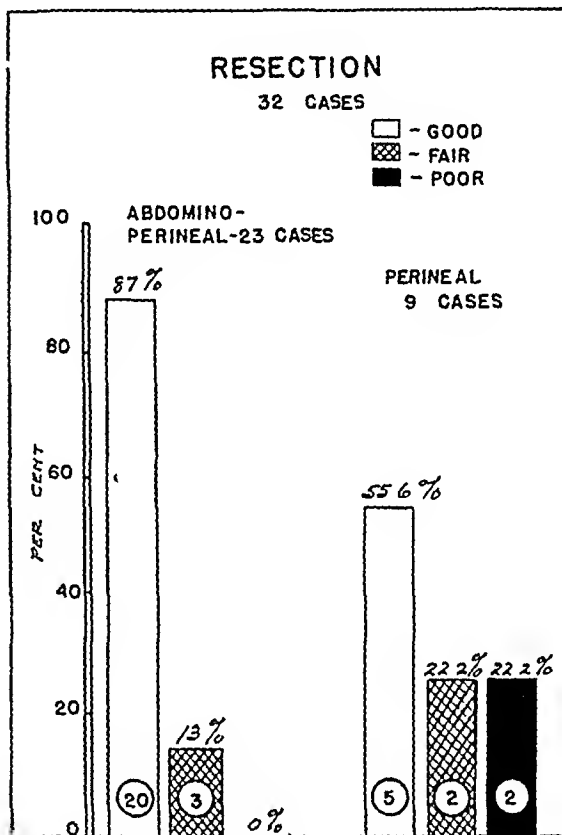


CHART 4—Contrast of results in abdomino-perineal resection (Miles or Lahey) and perineal resection (Lockhart Mummery)



limited, we have not seen resolution of firm, fibrous strictures as reported by some authors<sup>5, 6</sup>

Antigen therapy has been recommended for all forms of the disease, but published reports offer little encouragement for treatment of rectal stricture by this method. Our experience with antigen therapy has been negligible.

Dilatation has been widely used. It affords temporary relief of obstructive symptoms in the great majority of patients, although the risk of exacerbating the infection or perforating the bowel is commonly recognized. Our experience includes seven deaths attributable to this procedure.

With an inflammatory rectal stricture that does not respond to conservative measures, colostomy may be expected to eliminate obstruction and, in many patients, to mitigate the inflammatory symptoms. Forty-one per cent of such patients in our series were improved by simple colostomy. In comparing this with the resected cases, of whom 94 per cent were improved it should be recalled that a higher percentage of "severe" cases were subjected to simple colostomy. This may account partially for the "poor" results in the latter group.

Several authors have reported radical removal of the diseased recto-sigmoid,<sup>13, 14, 15, 16, 17</sup> usually by perineal resection. Failures following this operation may be attributed to extension of the disease beyond reach of the perineal approach. The only "poor" results in our series of resections occurred with the perineal approach, because of persistent drainage from the perineum or from the distal colostomy loop. Twenty-three combined abdomino-perineal resections, of which 16 were in one stage, gave quite satisfactory results. Certain of these cases might have been managed with equal success by less radical methods. In the majority, however, the rapid restoration of the chronically ill patient to good health apparently justified such drastic treatment.

Although we have used the one-stage procedure more frequently we now believe that the first stage of an abdomino-perineal resection by the Lahey technic is the operation of choice. The patient is thus prepared for removal of the disease-bearing area by abdomino-perineal resection should continued severity of symptoms require it.

Development of squamous cell carcinoma has occurred three times in our series of 192 cases. These patients had been under treatment for three, four and seven years, and all had positive Frei tests. The incidence of 1.6 per cent in our series may be compared with 8.6 per cent in that of Barber and Murphy.<sup>18</sup> Although this complication rarely is mentioned by other authors,<sup>18</sup> it constitutes a further factor for consideration in the treatment of chronic inflammatory rectal stricture.

#### SUMMARY

An analysis of 192 cases of inflammatory stricture of the rectum treated at the Cincinnati General Hospital has been presented. Various methods of treatment have been discussed and the results noted. Thirty-five patients

were subjected to radical excision of the rectosigmoid with generally satisfactory results and without an operative death. It is emphasized that this method of treatment is indicated only after conservative methods fail.

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DISCUSSION—DR VERNON C. DAVID, Chicago, Ill. I have been interested and instructed by the Cincinnati group in their surgical approach to the management of involvement of the rectum by lymphogranuloma inguinale. A number of years ago, when I was more active at the Cook County Hospital, I examined a large number of patients having such lesions. A brief summary of our impressions would stress the fact that a small percentage had ever had a suppurating inguinal bubo. I have never been impressed with the theory that rectal involvement is due to lymph blockade but rather feel from the history and early pathology that the majority of patients have had a contact infection.

This impression is further augmented by the ulceration from this disease found on fingers and on the tongue. While most of the rectal lesions are sharply limited to the lower bowel, I have operated upon at least two patients who had segmental involvement of other areas in the colon, and one of these patients had concurrent epilepsy, which may have been due to meningeal involvement. I am strongly of the opinion that we are dealing with a constitutional disease with local lesions which are primary or arise from contact infection.

In stricture of the rectum we found that local applications, dilatation of the stricture, or treatment with tartar emetic were ineffective. Colostomy gives great relief to many patients but if local improvement was great and marked stricture had not developed, the reestablishment of local continuity resulted in immediate exacerbation of the local lesion in the rectum. We have observed a few patients who had operative removal of the stricture, with union of the bowel. Local recurrence was prompt.

Since the use of sulpha drugs many patients suffering with lymphogranuloma inguinale of the rectum have been markedly improved or cured. In recent years, two private patients with rectal stricture, one with a colostomy, and both with active ulceration of the rectum, have been cured by sulfanilamide. Their strictures have been successfully dilated and the colostomy closed and they have been under observation and well for almost three years. Unfortunately, all patients with rectal ulceration and stricture and with a positive Flier test have not been cured and it is this group of patients that colostomy failing to relieve their symptoms fall into the category discussed by the authors this afternoon. They have rendered a distinct service in bringing their experience to us and I have been favorably impressed by their arguments for radical removal of the lesion in a selected group of patients who have resisted all other methods of treatment.

DR C. ROLLINS HANLON (closing). I have little to add to what Doctors Woods and David have said, except to emphasize once more the dangers of dilatation. The safety of dilatation carried out in the Out-patient Department is in sharp contrast to the risk in the method we report, where the dilatation was carried out under anesthesia, with many fatal results.

Paradoxically enough, our review of these cases has led us to be more conservative than we might have been several years ago, since we realize that many cases will not need a combined abdominoperineal resection as we once believed, but rather, colostomy by the Lahey technic and treatment with the sulfonamides. If the results are satisfactory, leave them in that stage, and many of them get along very well.

INFLUENCE OF ESTROGENS ON THE PERIPHERAL  
VASOMOTOR MECHANISM\*

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THE EXPLRIMENTAL STUDIES forming the background for the present clinical report stem from an observation made by Maurice Raynaud, himself, in the first of the two patients described by him in his original classical exposition, in 1862, of the syndrome bearing his name

“Menstruation does not appear to have any influence upon the appearance of the phenomenon, *but it is a remarkable fact that the complete disappearance of attacks of local syncope has always been noted by this lady as the first index of a commencing pregnancy*” (Author’s italics)

Predicating the possibility that the physiologic mechanism underlying this observation of Raynaud was associated with estrogenic substances, one of us (McGrath), in 1933 conducted a series of experiments, and in 1935 submitted what is, to the best of our knowledge, the first published report of purely experimental work in this field<sup>1</sup>

Briefly, those studies consisted of an evaluation of the effect of estrogens upon experimentally produced peripheral gangrene in the tail of the albino rat. Such gangrene was induced by the parenteral administration of an adequate quantity of ergotamine tartarate. The resultant lesions having been studied grossly and microscopically (Figs 1-4), several series of animals, male and female, were set-up in parallel groups consisting of a control group, a similar group intoxicated with ergotamine tartrate, and a third group similarly intoxicated with eigotamine, but shielded by the daily administration of estrane in the form of theelin. It was observed (Tables I and II) that all unprotected animals developed gangrene of the tail

TABLE I  
MALES

A SUMMARY OF THE MALE RATS OF THE FIRST THREE SERIES. ERGOTAMINE WAS ADMINISTERED AS A SINGLE DOSE AT THE START OF EACH SERIES. THE THEELIN INJECTIONS AND THE PERIODS OF OBSERVATION WERE SYNCHRONOUS WITH CORRESPONDING SERIES OF FEMALES AS INDICATED IN TABLE II

	Series I Ergotamine 25 mg per Kg	Series II Ergotamine 40 mg per Kg	Series III Ergotamine 60 mg per Kg	Totals
Total rats	30	15	15	60
Normal control	10	5	5	20
Rats receiving ergotamine alone	10	5	5	20
Rats receiving ergotamine & theelin	10	5	5	20
Theelin in rat units daily	2	5	8	—
Gangrene in normal controls	0	0	0	0
Gangrene without theelin	10	5	5	20
Gangrene with theelin	10	5	5	20
Deaths	0	0	0	0

\* Read before the American Surgical Association, May 3-4, 1944, Chicago, Ill

All protected *male* rats also developed gangrene of the tail. Only two female rats, however, out of 40 protected with theelin, developed gangrene of the tail, and in these two the amount of gangrene was incomparably less than in the control animals. These findings were confirmed independently by



FIG 1—Gangrene of tail of rat intoxicated with ergotamine tartrate



FIG 2—Cross section of tail of rat after intoxication with ergotamine (200  $\times$ ) Note thrombosis of the central artery

TABLE II  
FEMALES

A SUMMARY OF THE FEMALE RATS OF THE FOUR SERIES    ERGOTAMINE WAS GIVEN IN A SINGLE DOSE AT THE START OF EACH SERIES    THEELIN INJECTIONS WERE CARRIED ON OVER PERIODS OF 30 DAYS, AS FOLLOWS

	Series I Ergotamine 25 mg per Kg	Series II Ergotamine 40 mg per Kg	Series III Ergotamine 60 mg per Kg	Series IV Ergotamine 100 mg per Kg	Totals
Total rats	30	30	30	30	120
Normal controls	10	10	10	10	40
Rats receiving ergotamine alone	10	10	10	10	40
Rats receiving ergotamine & theelin	10	10	10	10	40
Theelin in rat units daily	2	3	3	5*	—
Gangrene in normal controls	0	0	0	0	0
Gangrene without theelin	10	10	10	10	40
Gangrene with theelin	0	0	0	2	2
Deaths	0	0	0	1	1

\* The five rat units daily was the standard dose for this Series    In the four rats with trophic changes, ten rat units daily were given

Series I	Dec 8, 1933—Jan 7, 1934
Series II	Jan 15, 1934—Feb 14, 1934
Series III	March 1, 1934—March 31, 1934
Series IV	April 25, 1934—May 24, 1934

The rats were observed for an additional 20 days thereafter

Suzman, Freed and Prag,<sup>2</sup> and by Ratschow and Klosterman,<sup>3</sup> in 1938    The former investigators, following through a predication made by us, demonstrated further that in castrate male rats, the protective action of estrogens was quantitatively the same as it was in females    In the same year (1938) Reynolds<sup>4</sup> concluded from extensive investigations conducted in his laboratory, that the mode of action of estrogens was essentially that of local liberation of acetylcholine, that the estrogens were, in other words, cholinergic

This report represents our experience, during the past ten years, in translating the foregoing experimental studies into clinical therapeutics    Inasmuch,

TABLE III  
PERIPHERAL VASCULAR DISTURBANCES

- A Vasomotor or functional disturbances
  - I Vasoconstrictor disturbances
    - 1 Raynaud s syndrome
    - 2 Acrocyanosis
  - II Vasodilatory disturbances
    - 1 Erythromelalgia
    - 2 Acute painful osteoporosis
- B Organic diseases of the arteries
  - I Traumatic (chemical and thermal)
    - 1 Embolism and simple thrombosis
    - 2 Arteriovenous aneurysm
    - 3 Injuries from phenol and all caustics
    - 4 Frost-bite
  - II Inflammatory (toxic)<sup>1</sup>
    - 1 Thrombo-angutis obliterans
    - 2 Specific arteritis (syphilis)
    - 3 Non specific arteritis (examthemata, ty phoid)
    - 4 Non-specific arteritis (chronic toxemia, ergotism)
    - 5 Endarteritis obliterans (cause underermined)
  - III Degenerative changes
    - 1 Arteriosclerosis (senile diabetic)
    - 2 Monckeberg s medial sclerosis

as a wide range of peripheral vascular disturbances have been studied, it is necessary, for purposes of clarity, that some order be followed in discussing them. Classifications of diseases of the peripheral vascular system, based upon known or suspected etiologic factors have become fairly well standardized within the last decade (Table III). For diagnostic and, to some extent,

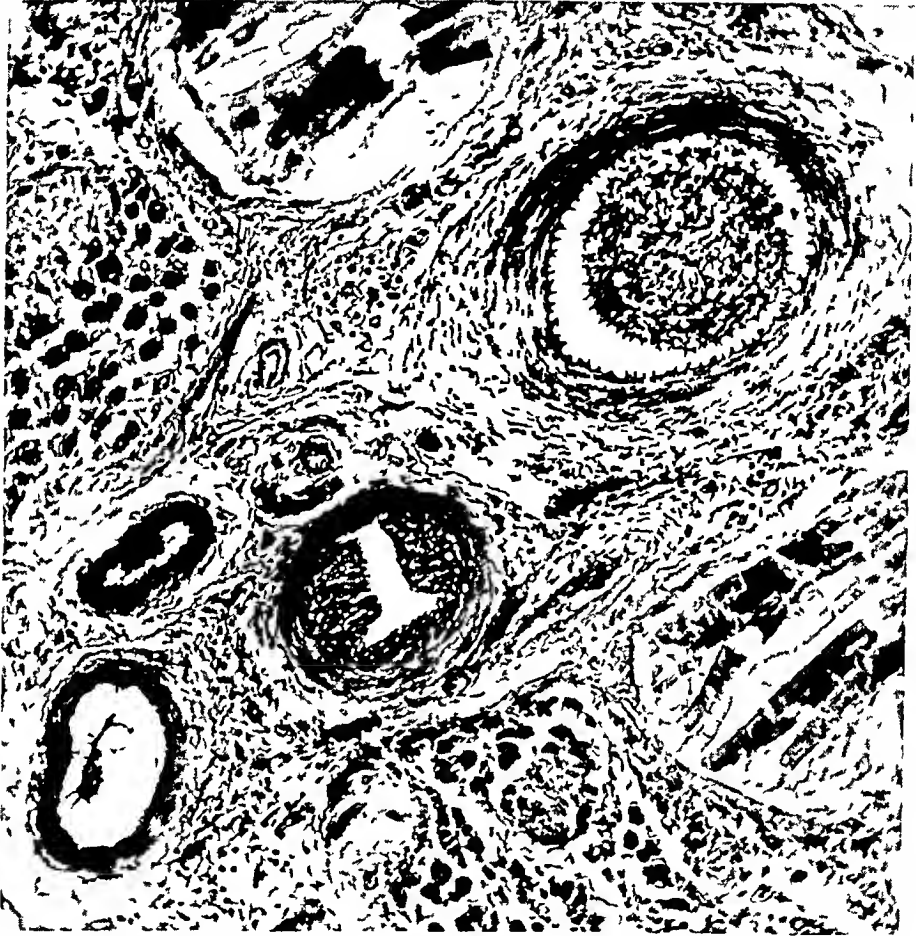


FIG. 3—Cross section of tail (200×). The intima of the central arteriole has proliferated markedly. The large vessel containing the thrombus is the main artery of the tail.

prognostic purposes, such classifications are indispensable. For purposes of therapy, however,—unless one is content with a nihilistic or defeatist approach to the problems—, such catalogues are either too cumbersome or, since they emphasize etiology alone, ignoring the pathologic physiology involved in these disease processes, too complex to be of any great value as therapeutic guides. We have found it advantageous, therefore, to regroup and greatly simplify the classification of diseases of the peripheral vascular tree as follows (Table IV).

It is obvious that such a classification, based as it is upon the pathologic physiology involved in the peripheral vascular disturbance, cuts rather sharply across the standard classification of such diseases. It is constructed as a therapeutic rather than an academic guide, and is intended to be an adjunct

to, rather than a substitute for, the customary classification of peripheral vascular diseases

Our experience during the past ten years has demonstrated that Group IV is composed in great part of those patients who originally belonged in

TABLE IV  
CLASSIFICATION

Group I	Primary vasomotor disturbances
	A Raynaud s syndrome
Group II	Primary structural vascular diseases with secondary vasomotor disturbances
	A Thrombo-angitis obliterans
	B Arteriosclerosis obliterans
	C Acute arterial occlusions
	D Chronic long-standing phlebitis
Group III	Primary vasomotor disturbances with secondary structural vascular changes
	A Raynaud s syndrome with trophic changes in digits
Group IV	Primary and predominantly structural vascular diseases
	A Advanced arteriosclerosis obliterans

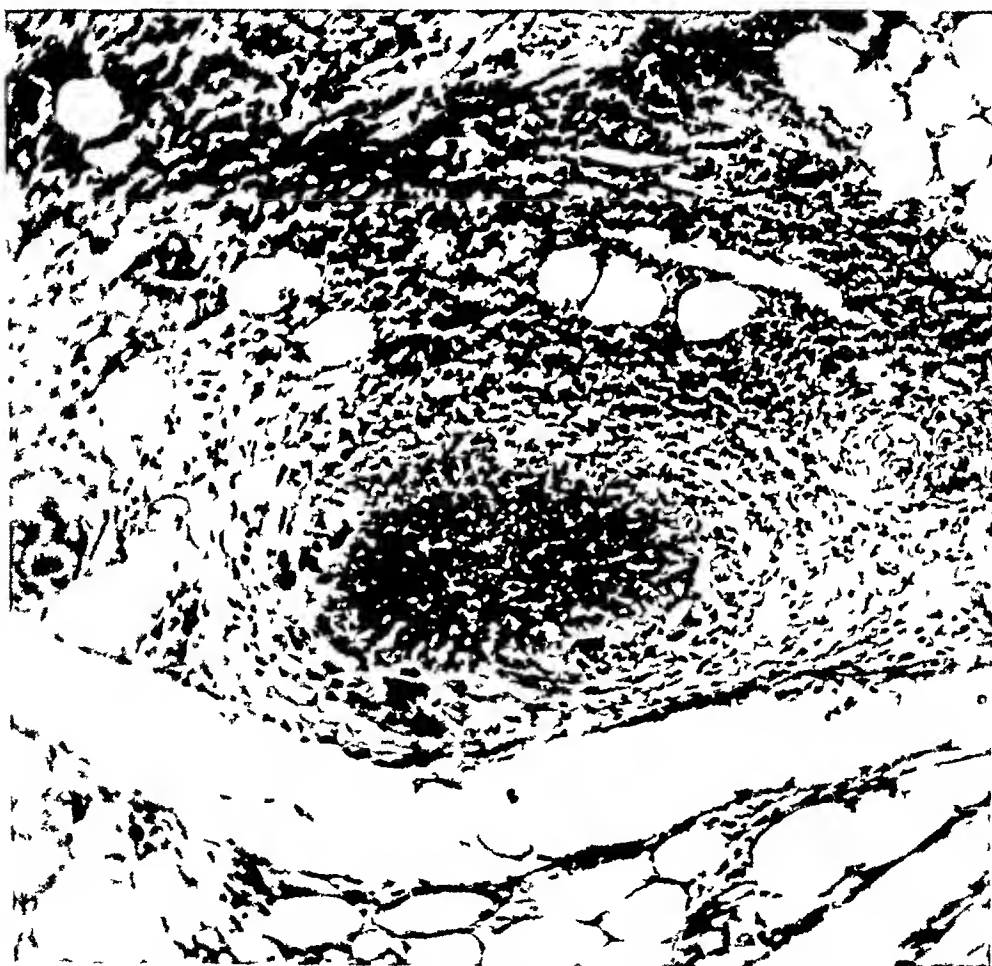


FIG 4.—Cross section of tail (200 X) Area of thrombophlebitis The thrombus, the walls of the vessel, and the perivenous tissues are invaded with polymorphonuclear leukocytes

Group II but in whom the organic lesion has progressed to the point of involving practically the entire arteriolar bed of the involved extremity or extremities, thereby, so completely dampening the effective operation of the autonomic vasomotor control mechanism as to render its influence negligible These patients, we feel, should be eliminated promptly from the present dis-



cussion by the frank admission that we have failed in treating them with this or any other form of therapy to help them either subjectively or objectively. On the other hand, Group III patients represent, for clinical purposes, an extension of and exaggeration of the phenomena observed among patients composing Group I. Their segregation into a special class is warranted only by the quantitative difference in the problem presented. We have preferred to discuss all such patients under the single heading of Group I. Furthermore, in concert with most present day clinicians, we have felt that efforts to subdivide primary vasospastic disturbances into numerous "named" diseases are both confusing and at variance with current opinion concerning the pathologic physiology involved in these syndromes. As a generic term we have made use of the appellation "Raynaud's syndrome."

In 1940, we submitted the first report of our experience with patients belonging in Group II. In that discussion, we limited ourselves to patients suffering from active inflammatory disease of the peripheral vascular tree. Even before that time, however, our own experience corroborated that reported by other clinical investigators, namely, that in the majority of cases of early and moderately advanced degenerative arterial disease the influence of the vasomotor mechanism was far from negligible. It is impossible, in the time available, to adduce the accrued evidence in support of this thesis except by bibliographic reference. Suffice it to say here, that the significant rôle played by the vasomotor mechanism in degenerative disease of the peripheral arterial tree is today a well established and accepted clinical entity. It would be superfluous, also, to elaborate upon the profound rôle played by the vasomotor control mechanism in acute arterial occlusion.

The subgroup designated "chronic long-standing phlebitis" requires some explanation. By definition, we have included in this category only patients whose phlebitis is of more than one year's duration. In many instances, the process had been present for upwards of ten years. By definition, also, we have included only patients in whom the inflammatory process was recurrently active. Such patients experienced intermittent episodes of pain, burning, and a sense of heaviness in extremities which were chronically swollen, indurated, discolored and in many instances ulcerated. This excludes, on the one hand, recent, acute thrombophlebitic or phlebothrombotic processes, and, on the other, the phlegmasia of old phlebitic processes in which active inflammation was no longer a factor. We feel that we are not alone in the belief that, in such patients as are herein classified, the element of vasomotor imbalance is a not inconsiderable one.

On quite a number of patients in each group, we have made repeated instrumental vasomotor studies, using both the elaborate technic of alternation of total environmental temperature conditions, as well as the simpler and more practical vasomotor index tests of Coller, and of Landis. In those patients on whom such studies were made, we found both before and after the use of estrogens, the tests, in great part, paralleled the clinical picture. Because, however, of the very narrow margin between peripheral circulatory

competency and incompetency in many of the patients with primarily organic arterial disease, evaluation of the changes found by vasomotor test has been extremely difficult. And in view of the sharp clinical alterations observed we have felt justified in omitting from the present brief discussion, data relative to these tests.

The form in which estrogenic substances have been used has varied over the ten-year period as the field of choice has widened with the successful synthesization of estrone and its esters. At first we used estrone as theelin, initially in aqueous solution, later in oil, and more recently as an aqueous suspension. When  $\alpha$ -estradiol was introduced, we tried it in the form of its benzoate ester, both as Ben-ovocylin (Ciba) and as Progynon B (Schering). Neither of these seemed to be quantitatively satisfactory from clinical observations. With the development of  $\alpha$ -estradiol dipropionate, however, at the advice of and with the most generous cooperation of the Ciba Corporation, we changed to this substance (Di-Ovocylin). The results were most gratifying and for the past two years we have used it exclusively in the treatment under discussion. Dosage has been empirical and individual. For the most part, we have found the minimal effective dosage to be 0.5 mg given three times weekly for a period of eight weeks. In quite a few instances, however, it was necessary to increase this to 1.0 mg given at the same interval. In retrospect, moreover, we feel that the cases hereinafter reported as failures might have benefited by the use of larger dosage such as 2.5 or 5.0 mg.

Such large amounts, however, in the light of our present knowledge, cannot be used without great caution. With women in particular, we found it necessary to be more cautious, because of the primary effect of estrogens upon the genital organs. It should be noted, however, that in women still in active menstrual life, suffering from vasomotor imbalance, there is almost always a pronounced tendency to hypomenstrual function, with the result that the critical range of tolerance in the administration of estrogens to these women is really much wider than might be anticipated. By way of caution, however, we have limited our initial trial dosage in women prior to menopause, to 1.0 mg three times weekly, increasing this only in rare instances. The customary precautions regarding the breasts and genitalia, were observed here as in any administration of estrogenic substance for any purpose. In only one instance was a serious complication encountered. In that patient it was impossible to control increasing attacks of severe angiospasm with doses small enough to avoid serious menorrhagia. Ultimately, we removed her uterus transvaginally, and following her uneventful recovery, continued to use estrogen at an adequate level. The uterus failed, on minute gross and microscopic examination, to reveal any evidence of malignant change.

This report extending over the ten years ending January 1, 1944, includes 345 patients, distributed as in Table V. A few additional comments should be appended to the data contained in that analysis. Group 1-A includes 13 women long past their menopause, in whom the vasospastic phenomena developed quite suddenly and progressed with unusual rapidity.

TABLE V  
ANALYSIS OF DATA

		Total Number of Patients			345
		Total Patients	Males	Females	Age Range    Average Age
Group I					
	Raynaud's syndrome	163	66	97	14-67    37 years
Group II					
	Thrombo-angitis obliterans	34	34	0	22-47    37 years
	Arteriosclerosis obliterans	48	35	13	42-83    58 years
	Acute arterial occlusions	26	20	6	24-67    52 years
	Chronic long standing phlebitis	74	18	56	23-69    40 years

In them, the response to estrogen therapy was gratifyingly prompt and, apparently, complete. This category (Group I-A) contains, also, six patients in whom severe trophic changes had occurred in the fingers (Group III).

Group II-B requires further comment. In these patients, most of them past middle age, whose disease involved the lower extremities, every effort was made to provide satisfactory static correction of the feet, before the present therapy was instituted. In about 33 per cent of all patients of this age-group (45-70) seen, such orthopedic correction of the feet eliminated the patient's symptoms. Such patients were not included in this series. It should be noted, however, that while such correction apparently did not give subjective relief to the patients included in the present report, when such correction was omitted, the amount of estrogen necessary to be effective was noticeably greater, and *vice versa*. In all instances meticulous hygiene of the extremities, particularly the feet, was instituted and its observance by the patient insisted upon.

TABLE VI  
END RESULTS

		Unsatisfactory	
	Satisfactory	No	Other Therapy
Group I		2	
	Raynaud's syndrome	160	1    Sympathectomy
Group II		4	Unknown
	Thrombo-angitis obliterans	29	1    Amputations
	Arteriosclerosis obliterans	48	0    Unknown
	Acute arterial occlusions	24	2    Amputations
	Chronic long standing phlebitis	69	5    Unknown

Table VI summarizes the results of estrogen therapy in these 345 patients. Necessarily, the significance of the designation "satisfactory," varies with the groupings. Briefly, the criteria used in determining a satisfactory result were as follows:

1 Raynaud's Syndrome. Cessation of episodes of "local syncope", termination of activity in trophic lesions, when present, return of the involved extremities to normal color, texture, and local temperature, cessation of sensory disturbances, and ability of the individual to withstand cold weather without abnormal changes in the involved extremities.

2 Thrombo-angitis Obliterans. Termination of activity of the inflammatory process when present, freedom from recurrences for not less than two

years, or, at least, the ability to abort an incipient attack by the prompt administration of estrogen therapy

3 Arteriosclerosis Obliterans. Elimination of intermittent claudication, painful feet, subjective coldness of the feet, and, when present, cessation of gangrenous processes involving the toes, without further spread.

4 Acute Arterial Occlusion All these patients were treated with passive vascular exercise, in addition to the administration of estrogenic substance. The term "satisfactory result" indicates here that in comparison to a similar group treated with Pavaex alone, there was, in these patients, a reduction of approximately 50 per cent in the time required for the involved extremity to reach a safe level of circulatory efficiency.

5 Chronic, Long-standing Phlebitis. Cessation of pain and discomfort, healing of all ulceration and dermatitis, elimination of all discoloration except permanent pigmentation of the skin, disappearance of brawniness and induration of tissues, and an appreciable reduction in swelling of not less than six months' duration. We have never been able to eliminate all such edema.

As suggested heretofore, we suspect that some of our failures might have been avoided, had we been willing at that time to use larger doses of Di-Ovocylin. Such a conjecture obviously does not apply to the two cases of acute occlusion, nor to the five cases of chronic phlebitis.

#### SUMMARY

The experimental background for the clinical use of estrogenic substances in the treatment of peripheral vascular disease is presented.

A series of 345 patients, so treated over the past ten years is presented, and the results analyzed.

In all these patients vasomotor disturbances played either a primary or at least a major secondary rôle.

The results of these clinical studies indicate, we believe, that in estrogenic substances, we have a powerful therapeutic agent for the treatment of peripheral vascular disturbances in which there is a significant component of vasomotor imbalance.

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DISCUSSION —DR LOUIS G HERRMANN, Cincinnati, Ohio In the management of circulatory disturbances in the extremities we must not lose sight of the fact that many of the serious complications are the direct result of the severe secondary vasospasm

We believe that excessive smoking, especially in young women, is largely responsible for the increase in the incidence of serious vasomotor instability in the extremities. The circulatory disturbances which are associated with severe peripheral vasospasm present important therapeutic problems and whenever we disregard the early signs and symptoms of this syndrome we simply encourage the development of the more serious sequelae, such as trophic and ischemic changes in the digits.

We are convinced that these patients must abstain from the use of tobacco in all forms if permanent benefits are to be expected.

Vasodilating drugs, with the exception of alcohol, are of little therapeutic value and sympathectomy should be reserved for the severe varieties of the Raynaud syndrome which do not respond to conservative treatment.

The prolonged vasodilatation which results from intramuscular injection of synthetic estradiols, through their liberation of an acetylcholine-like substance in the tissues, has provided us with an effective means of controlling peripheral vasospasm.

The method of treatment which Doctor McGrath has described does not displace any of the accepted methods of treating the primary cause of vasospasm, and we present these data simply to support the contention that the synthetic estrogens are valuable adjuvants in the management of primary and secondary vasospasm in the extremities of both men and women.

# MODIFICATION OF THE KING OPERATION FOR BILATERAL VOCAL CORD PARALYSIS\*

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WE WISH TO PRESENT a modification of the King<sup>1</sup> operation for bilateral cord paralysis. As is the case in most original contributions, others have found difficulty in fulfilling all the principles laid down by the author, even after numerous dissections of unembalmed cadavers in the anatomical laboratory. We believe that all credit should go to King for his contribution in this field, and in no way wish to detract from his work in this presentation, merely to present a modification which we believe simplifies his procedure. Eleven cases have been operated upon employing this modification. The diagnosis of bilateral cord paralysis has been corroborated by the laryngologist in all cases. It is not the purpose of this paper to discuss symptomatology or diagnosis of the bilateral paralysis of the vocal cords. All the cases reported followed thyroidectomy, and in three cases two thyroidectomies had been performed.

The operation to be described has been carried out under sodium pentothal local anesthesia. Tracheotomy has been performed in those cases not already canalized at least five to 14 days before the plastic operation. This depends upon the patient's adjustment to the tracheotomy tube and the degree of irritation it produces. We have utilized a low transverse incision for the insertion of the tracheotomy tube because it interferes less with the second stage, or plastic procedure, and also for cosmetic reasons.

The patient is placed with head in hyperextension and in a position that the laryngologist can readily visualize the larynx by direct laryngoscopy when the cord is abducted. The tracheotomy tube is removed and, after preparation of the neck, a sterile tracheotomy tube is placed in the trachea. Continuous oxygen is administered through a sterile catheter inserted in the tracheotomy tube.

A transverse incision is made at the level of the middle third of the thyroid cartilage and the flaps dissected upward and downward. The fascia and pregladular muscles are divided longitudinally to either side of the midline depending on which side is to be approached. The dissection is carried down to the lateral wing of the thyroid cartilage (Fig A). A portion of the superior pole of the thyroid, with scar tissue, is usually encountered at this step and will require resection with control of the superior thyroid vessels.

The thyroid cartilage is now rotated medially with a hook retractor. This exposes, and puts on tension, the inferior constrictor of the pharynx.

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\* Read by title before the American Surgical Association, May 3-4, 1944, Chicago, Ill

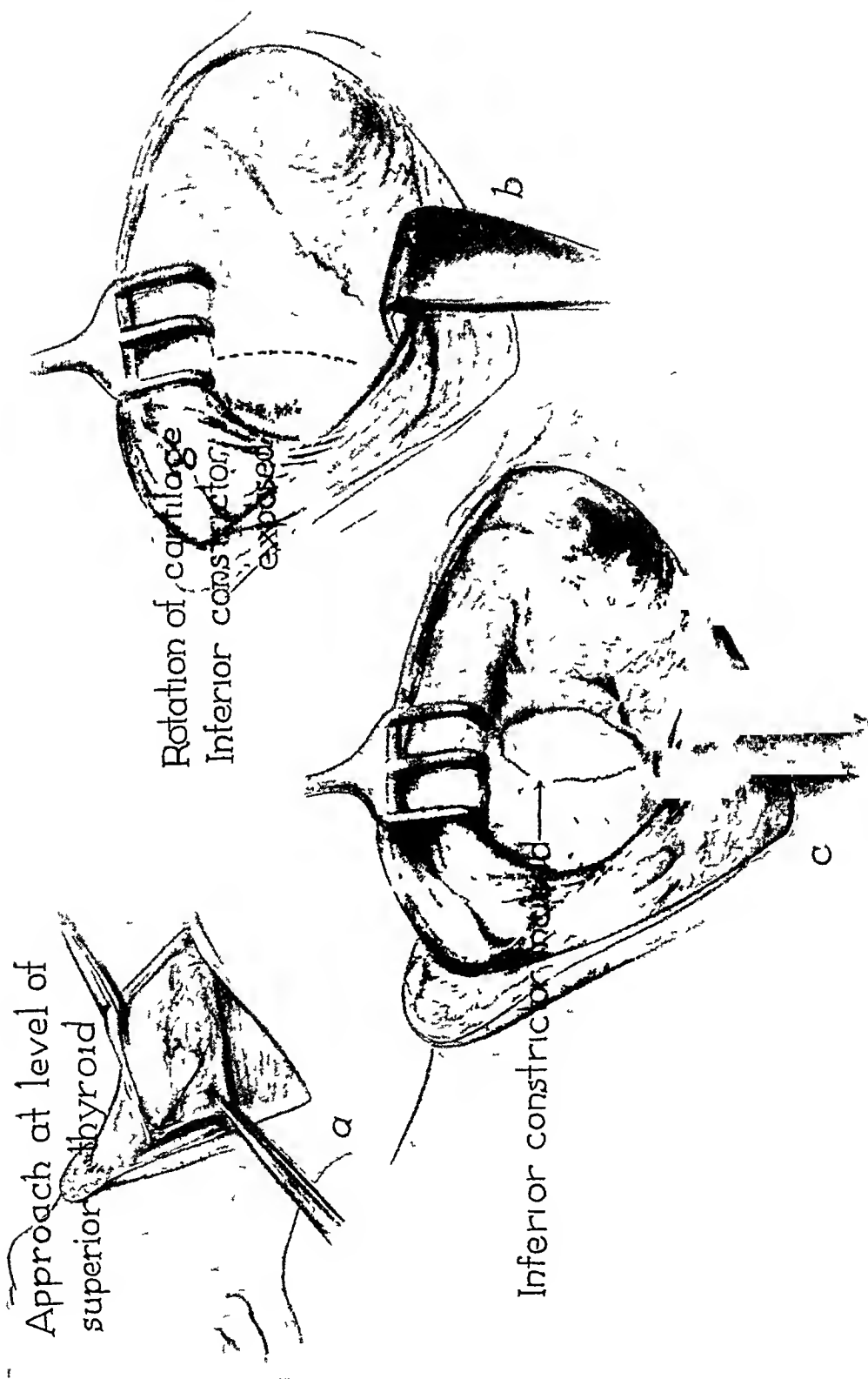


FIG. 1



C



B



A



F



E



D



I



H



G





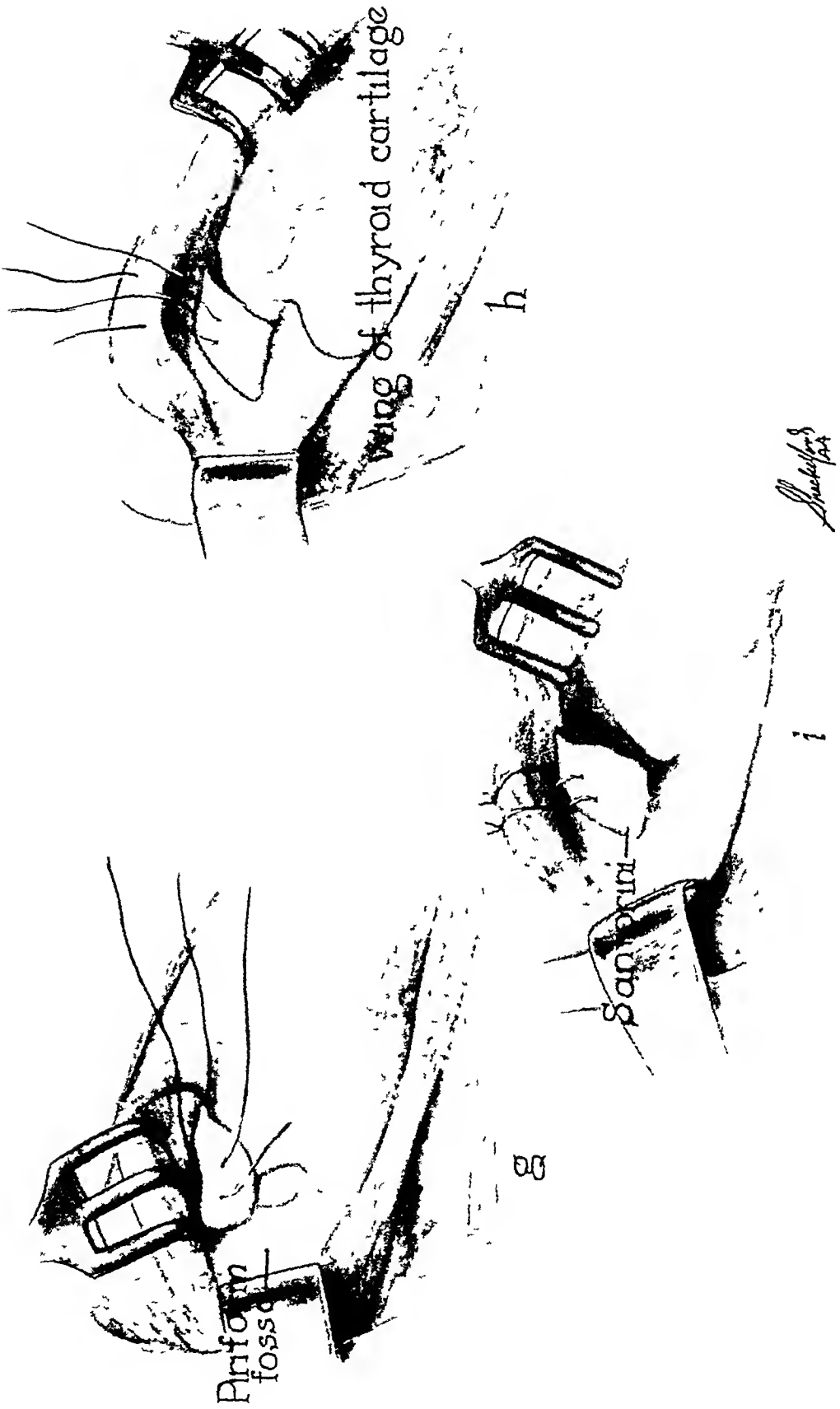


FIG. 2

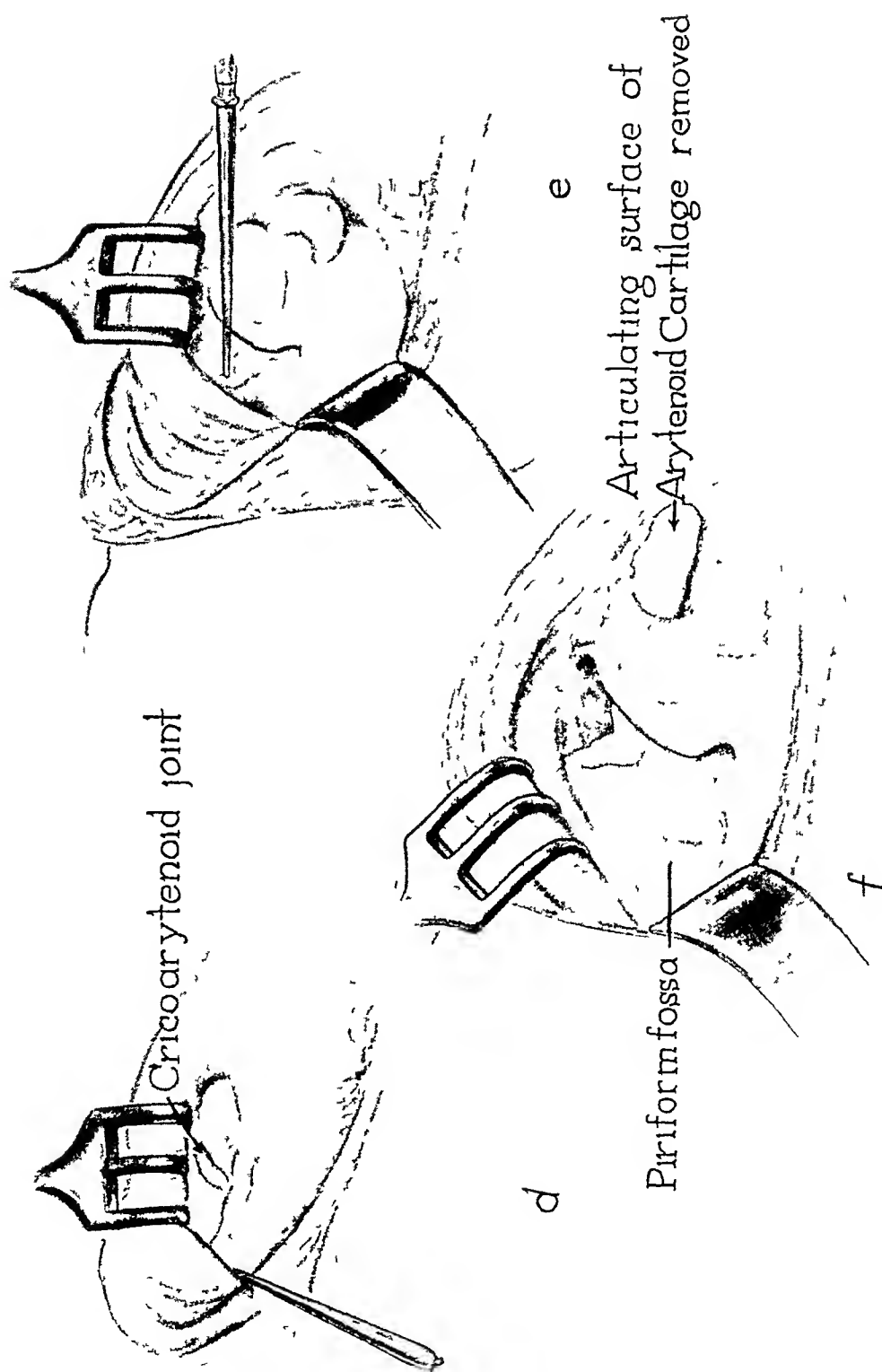


FIG. 3

(Fig B) The crico-arytenoid joint is readily palpated through the inferior constrictor muscle. An incision is made through the constrictor muscle at the level of the crico-arytenoid joint (Fig. C)

The joint capsule is now opened, using a No 15 Bard-Parker knife (Fig D). In the patient with bilateral cord paralysis the space between the articulating surfaces of the cricoid and arytenoid cartilages is definitely widened. A dural hook is placed in the arytenoid cartilage and the capsule of the joint further divided laterally and posteriorly (Fig E). The mucous membrane posterior to the cartilage at the pyriform fossa is displaced by blunt dissection. This exposes the muscles on the posterior surface of the arytenoid cartilage (Fig F). The separation of these structures on the posterior surface is not complete until the tip of the arytenoid cartilage is seen.

Two alloyed steel wire (No 35) sutures are placed through the arytenoid cartilage using a No 4 Lane cleft palate needle (Fig G). The first suture is placed about 3 Mm above the articulating surface of the arytenoid cartilage and the second similar distance above the first (Fig G). The articulating surface of the arytenoid cartilage is then removed by curved scissors (Fig F), using the sutures to control the cartilage. Care must be exercised in the insertion of the sutures, as many of these cartilages are quite friable. If the cartilage is friable the sutures may be passed around the cartilage. The sutures are then threaded on a heavy sharp-cutting edged needle and passed through the lateral wing of the thyroid cartilage at the level of the crico-arytenoid joint (Fig H).

The thyroid cartilage is returned to its normal position and the sutures are drawn rather firmly but not tied. The laryngoscopist estimates the relative position of the cords by direct laryngoscopy. If the cord is not sufficiently abducted, greater tension may be applied to the sutures. When satisfied that sufficient abduction of the cord is obtained the sutures are tied (Fig I). Recheck of their position by the laryngologist after tying the sutures assures a satisfactory result. The resection of the articulating surface of the arytenoid cartilage facilitates placing the cord in abduction. The opening in the inferior constrictor muscle of the pharynx is closed with mattress sutures of No 000 chromic catgut. A Penrose drain is placed to this level and the wound closed in layers with similar suture material. Clips are used to close the skin.

The postoperative course is usually complicated by difficulty in swallowing due to the edema in the region of the pyriform fossa and the cord. This usually subsides within four to five days. The tracheotomy tube may be plugged, or corked, for progressively longer periods after the edema subsides. We have removed the tracheotomy tube as early as the sixth postoperative day. The average time has been 10.7 days for the permanent removal in all cases. Several patients have been discharged with their tracheotomy tube because of their anxiety state when the tube remained corked. All patients except one are actively engaged in their daily work without their tracheotomy tube. The patient who still has her tube had previously been operated upon

elsewhere, and the King procedure performed. She has not had complete relief, although after the operation the tracheotomy tube was removed and the patient experienced difficulty in breathing only when she was in the prone position.

The voice in all cases but two is good and in both of these is improving, one under voice training. The latter two patients were operated upon for correction of their bilateral cord paralysis less than a year after thyroidectomy. We believe that the compensatory action of the false cords has not had sufficient time to develop in these two patients, thus, accounting for their poor voices. Furthermore, we believe that the plastic operation should not be attempted too early following thyroidectomy. We now follow the rule of waiting at least one year. It may be possible to see partial recovery of one cord during this period—and the operation not necessary. An adequate air-way has been obtained in all but the one case referred to above. These patients have been observed from six months to five years after permanent removal of the tracheotomy tube. It is of interest that all the patients with an adequate air-way following the operation have developed a rather definite hypothyroidism. This varies in degree but responds to thyroid therapy. The sincere gratitude of these patients, as King has stated, is like none encountered in any other group of patients. This is particularly true of the patients who have worn a tracheotomy tube for years.

#### CONCLUSIONS

We have presented a modification of the King operation for bilateral vocal cord paralysis. We believe the procedure warrants consideration because. First, its simplicity, second, one side provides sufficient and adequate air-way for removal of the permanent tracheotomy tube, and third, sufficient time has elapsed to evaluate the procedure.

We wish to thank Dr. T. B. McCullough, of the Department of Otolaryngology, for his invaluable help in these operations.

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# CONGENITAL ATRESIA OF THE ESOPHAGUS WITH TRACHEOESOPHAGEAL FISTULA\*

RECONSTRUCTION OF ESOPHAGEAL CONTINUITY BY PRIMARY ANASTOMOSIS

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IN THE ANOMALY of congenital atresia of the esophagus, a dysplasia that is more extensive than an atresia is found at a level corresponding to the junction of the upper and middle thirds of the esophagus. The upper portion of the esophagus ends as a blind pouch in almost all instances. The upper end of the lower esophageal segment usually enters the trachea, thus forming a tracheoesophageal fistula, this occurred in 29 of the 32 patients in this series. The condition is incompatible with life, as feedings can not enter the stomach. Furthermore, the feedings and accumulated secretions in the blind upper segment overflow into the trachea, and death soon results from aspiration pneumonia. The surgically ideal plan for the correction of the anomaly is one that accomplishes ligation of the fistula and reestablishment of esophageal continuity by a primary anastomosis of the esophageal segments. This article will be concerned primarily with the anatomic problems and surgical experiences that have been encountered in 24 patients for whom an exploration of the anomaly was undertaken. Reconstruction of the esophagus was accomplished in 16 patients, of whom six are now living from seven months to three years and one month after operation.

## THE ANATOMIC PROBLEM

The suspicion of a congenital obstruction of the esophagus is aroused by attacks of choking, dyspnea and cyanosis on attempts to swallow fluids. An actual obstruction of the esophagus can be demonstrated by the inability to pass a catheter into the stomach. To be certain that the obstruction is complete, iodized oil is given by mouth under fluoroscopic observation. A dilated blind upper esophageal segment, terminating usually at the level of the second or third dorsal vertebra, is then evident. In all the 32 cases in this series, the upper segment ended as a blind pouch. In an additional recent case of tracheoesophageal fistula without esophageal atresia, the esophageal lumen was patent and of normal caliber, but a fistulous communication was present between the trachea and the esophagus.

In the presence of a verified complete obstruction of the upper esophagus, the existence of air in the stomach is indicative of a communication between the lower esophageal segment and the trachea or a bronchus. Air was noted

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\* Read before the American Surgical Association, May 4, 1944, Chicago, Ill

in the stomach or intestines in 26 of the 31 cases studied by roentgenologic examination, and air was present in the stomach before operation in 20 of the 24 patients for whom a thoracic exploration was undertaken. An anastomosis was performed in 15 of the patients with air in the stomach and could have been performed readily in another similar case, thus demonstrating the fact that an anastomosis was possible in 80 per cent of the patients in whom the diagnosis of a tracheoesophageal fistula could be made by the preoperative roentgenologic examination.

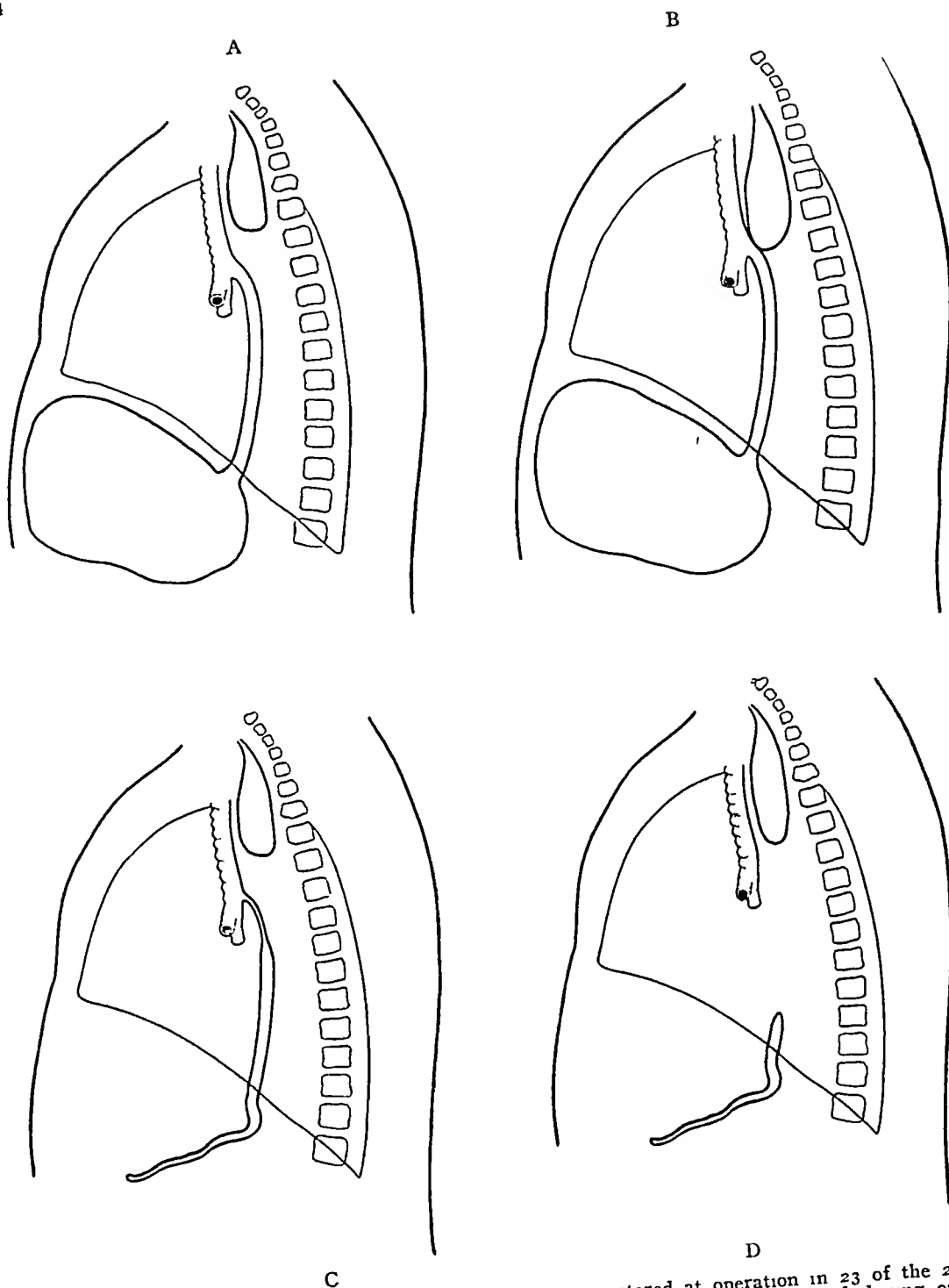
The absence of air in the stomach is suggestive, but not necessarily diagnostic, of an absence of a tracheoesophageal fistula. Of the five patients without air in the stomach two patients had a small but patent fistulous communication between the lower esophageal segment and the trachea. In another patient, the exact condition of the lower segment could not be ascertained as surgical exploration was not performed and a postmortem examination was not made. The two remaining patients had an actual agenesis of the esophagus, in that the lower segment of the esophagus extended for only about 1.5 cm above the level of the diaphragm. Operation was performed in four of the five patients without air in the stomach and an anastomosis was possible in only one case (25 per cent).

The absence of a tracheoesophageal fistula can also be determined by bronchoscopic examination, as advised by Shaw.<sup>22</sup> A preoperative diagnostic bronchoscopic examination has not been undertaken in this clinic as yet, because it has been believed that the final criterion for operability depends upon the result of surgical exploration of the anomaly. It has been definitely established that a fistula was absent in only two of the cases, both were operated upon recently and in both there was agenesis of the lower esophageal segment. In view of this correlation, it would appear that the absence of a fistula which is suspected by the absence of air in the stomach and which could be confirmed by bronchoscopy, is highly suggestive that an anastomosis cannot be done.

The diameter of the upper esophageal segment is usually between 1.2 and 1.5 cm. Although the diameter has been slightly less than 1 cm in several instances, it has always been of ample size to permit an anastomosis. The length of the upper segment is of greater significance than its diameter, as a short upper segment may interfere considerably with the performance of an anastomosis. If the upper segment is short, and if the lower segment reaches only to the tracheal bifurcation or to a main bronchus, the difficulties are augmented. The gap between the two segments has usually varied between 1.5 and 3 cm before an attempt has been made to approximate them. Partial muscular continuity of the two segments without any separation between them has been present, however, in five of the 24 patients for whom an exploration was performed. In these cases the muscular attachment was divided and the fistula was ligated at a high level before making the anastomosis.

An unusually narrow diameter of the lower segment, a short length of the

# ATRESIA OF ESOPHAGUS



**FIG. 1**—The types of the anomaly that have been encountered at operation in 23 of the 24 cases from whom exploratory operation was performed are illustrated (One patient died during operation before the nature of the lower segment was determined)

(A) The most frequent type of malformation of the esophagus. The upper esophagus ends as a blind pouch. The lower esophagus arises from the trachea at a level that is usually between 0.5 and 1 cm above the bifurcation of the trachea. Air is present in the stomach indicating the presence of a tracheoesophageal fistula. This type of anomaly was present in 13 of the 24 patients from whom a primary exploration of the anomaly was performed. Variations in the location of the fistula were found, and in two cases the lower esophagus arose from the right stem bronchus.

(B) Partial muscular continuity of the two segments. The anomaly otherwise is the same as in A (five cases).

(C) The lower segment is greatly contracted for a variable distance below its origin from the trachea and air has not entered the stomach, although a tracheoesophageal fistula was present (two cases). In a third case, the lower segment was contracted, but air was present in the stomach (not illustrated) (Figures 1, A, B, and C, Haight and Towsley,<sup>5</sup> By permission of Surgery, Gynecology and Obstetrics).

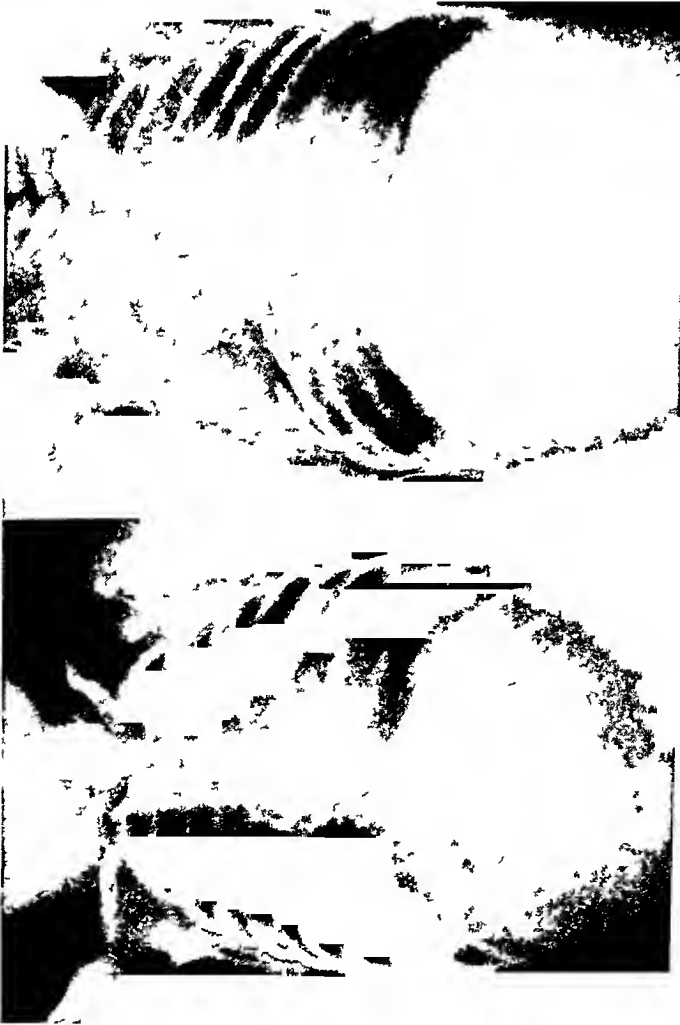
(D) Atresia of the upper esophagus and agenesis of the lower esophagus. The stomach does not contain air (two cases).





C

(C) Autopsy showed agensis of the lower esophagus which extended for a distance of only 1.5 cm above the diaphragm. In the photograph the short length of the lower esophagus and the entire stomach and duodenum are seen. A narrow strand of fibrous tissue extended upward from the lower esophagus for a distance of several centimeters. The stomach is greatly contracted and a Carrel tube has been inserted into the gastrostomy opening to demonstrate its location and the small size of the stomach.



B

A

Fig 2—R R, Case 25 (A) Admission roentgenogram showing absence of air in stomach and intestines. The upper esophageal segment has been visualized by the ingestion of iodized oil. The amount of the oil has been carefully limited, and no oil has entered the trachea or lungs. (B) Roentgenogram two days after operation. The right extrapleural approach was used and the extent of the costal resections (ribs 3, 4 and 5) is seen. The lower esophageal segment was not found, and a gastrostomy was done five days after the extrapleural operation. Death occurred on the fourteenth postoperative day from lobular pneumonia.

lower segment (agenesis), and a low position of the tracheoesophageal fistula have been the important factors in preventing an anastomosis from being made in six of the seven patients for whom an anastomosis could not be performed. The diameter of the lower segment is usually between 5–7 Mm. In two cases the diameter was so small (3–4 Mm) that it was technically impossible to construct an anastomosis. In the two cases of actual agenesis of the lower segment, the lower segment extended for such a short distance above the diaphragm that it could not be found within the field of operation (Fig. 2).

The lower margin of the tracheoesophageal fistula is most often situated about 0.5 to 1.0 cm above the tracheal bifurcation. When the lower segment is short and the tracheoesophageal fistula is present at the level of the tracheal bifurcation, or if the lower segment enters one of the main bronchi, the chance of obtaining a satisfactory anastomosis has been less than when the lower esophagus enters the trachea at a higher level. In two of the six cases for which an anastomosis could not be done, the fistula was located lower than usual. In one of these patients the lower segment extended directly downward from the tracheal bifurcation, and in the other case it arose from the right main bronchus. It was possible, however, to complete an anastomosis in another patient in whom the fistula arose from the right stem bronchus. In view of this case, it may be seen that the preoperative determination of a low position of a fistula, as might be determined by bronchoscopy, does not definitely exclude the possibility of an anastomosis. It is believed, therefore, that an exploratory operation offers the final criterion regarding the possibility of a satisfactory reconstruction of the esophagus in those cases in which the presence of a tracheoesophageal fistula is evident from the fact that air is seen in the stomach. The seventh patient for whom an anastomosis was not done died as a result of injury to the aorta before the lower segment could be identified.

#### THE SURGICAL PROBLEM

The surgical problem is essentially a threefold one involving the correction of the esophageal obstruction so that aspiration pneumonia will not occur, ligation of the tracheoesophageal fistula so that gastric contents can not enter the trachea, and the provision of some means for feeding the infant. The early attempts to treat this condition surgically have been discussed in a previous communication.<sup>5</sup> Gastrostomy alone failed because of regurgitation of the gastrostomy feedings into the trachea. Various methods have been employed for interruption of the lower esophageal segment in conjunction with, or supplementary to, gastrostomy<sup>1, 3, 4, 12, 15, 17, 18, 20, 24, 25</sup>. These methods have largely been supplanted by two plans that are now fairly well standardized, insofar as surgical principle is concerned.

One plan, the indirect approach, consists of a three-stage procedure, *i.e.*, (1) extrapleural ligation of the tracheoesophageal fistula, (2) exteriorization of the upper esophageal segment, and (3) gastrostomy. This plan, which has

been used successfully by Leven,<sup>12, 13, 14</sup> Ladd,<sup>9</sup> and Humphreys,<sup>7</sup> anticipates the construction of an antethoracic esophagus at a later date so that feedings can eventually be taken by mouth. A modification of this plan has been suggested by Carter<sup>1</sup> and has been employed successfully by Nettrour.<sup>16\*</sup> The indirect plan was proposed<sup>12</sup> because it was believed that the operative mortality could be kept low by staging the operations and by avoiding the extensive extrapleural procedure that would be required by a primary reconstruction of the esophagus. Although it is logical to believe that this advantage should hold true, the three patients for whom the indirect method was begun in this clinic, died before the upper segment was exteriorized. The method was used by election in one of the early cases (Case 7) and by necessity in two subsequent cases (Cases 25 and 32). Had the upper segment been exteriorized without delay, the chance of success would probably have been greater. The indirect plan is, however, essential for the maintenance of life if the anatomic conditions are such that a primary reconstruction of the esophagus can not be done.

The other plan, a direct approach to the problem, consists of a reconstruction of esophageal continuity by a single stage extrapleural ligation of the tracheoesophageal fistula and a primary anastomosis of the esophageal segments. The direct plan of primary anastomosis was suggested in principle by Kieth<sup>8</sup> in 1910. The first reported operation of this type was described by Shaw in 1939,<sup>21, 22</sup> who also mentions a case in which the same technic was employed by Samson.<sup>19</sup> Lanman<sup>11</sup> had previously employed this procedure in four cases in 1936 and 1937. The first successful application of this plan was reported by Haight and Towsley<sup>5</sup> in 1943, and the patient is now living three years and one month after operation. The operation of primary anastomosis has subsequently been used successfully in five additional patients in this clinic, and all of the living patients are able to swallow through the reconstructed esophagus. Shaw,<sup>23</sup> Ladd,<sup>9</sup> Humphreys,<sup>7</sup> and Daniel<sup>2</sup> have also mentioned the successful use of this method.

The reconstruction of esophageal continuity by primary anastomosis represents the ideal surgical principle in the correction of the anomaly in that it allows the infant to swallow normally. Feedings by mouth can be started soon after the operation. If leakage of the anastomosis does not result in an external esophageal fistula or a recurrence of a tracheoesophageal fistula, further operations are avoided. The operative procedure is one of considerable magnitude for a new-born infant, but the infants have been able to withstand the operation considerably better than might be expected. The anatomic findings at the time of the operation will not always permit an anastomosis. An anastomosis was found to be possible, however, in 17, or 70.8 per cent, of the 24 patients for whom an exploration was performed.

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\* This patient was living and well at the age of two years and ten months. The antethoracic esophagoplasty has not as yet been performed. (Personal communication from Dr. C. J. Stoecklein, Pittsburgh, Pa., June 11, 1944.)

and it was possible in 16, or 80 per cent, of the 20 patients who had air in the stomach

The technical objection to the plan of primary anastomosis results from the fact that tension is invariably present at the site of the anastomosis. Tension occurs primarily because of the gap that often has to be overcome when the two segments are approximated. Less important causes of tension are the normal contractility of the longitudinal musculature of the esophagus and the normal mobility of the two esophageal segments. Observations during the preoperative roentgenoscopic examination, as well as during operation in the first several patients when local anesthesia alone was employed, have shown that the upper segment is displaced upward during swallowing, straining or

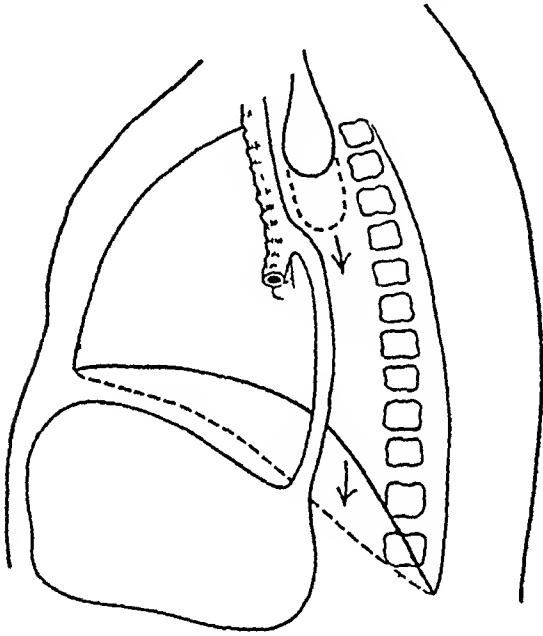


FIG 3

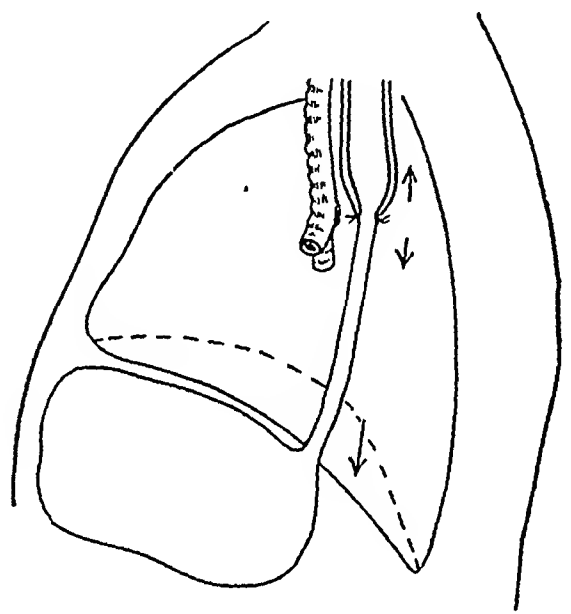


FIG 4

FIG 3—The mobility of the upper esophagus that is seen during roentgenoscopic examination is indicated by the position of the solid and dotted lines. Solid line indicates position of the upper esophagus during the expiratory phase of respiration and during straining and crying with their attending increase in intrathoracic pressure, dotted line indicates position of upper segment during inspiratory phase of respiration. Because of the mobility of the upper esophagus, roentgenoscopic observation allows a more accurate estimation of the position and length of the upper segment than does the roentgenographic examination.

FIG 4—Tension unavoidably occurs at the site of the anastomosis because of (1) the gap that usually must be overcome when the two segments are united, (2) the ascent of the upper esophagus during swallowing, crying and the expiratory phase of respiration, (3) the descent of the lower esophagus during the inspiratory phase of respiration, and (4) the normal contractility of the longitudinal musculature of the esophagus.

crying (Fig 3). The lower segment is normally pulled downward during the inspiratory descent of the diaphragm. Even though tension is not apparent when the patient is under general anesthesia during the operation, it is logical to assume that the mobility of the two segments exerts tension upon the anastomosis during the postoperative period (Fig 4).

The weak tensile strength of the wall of the underdeveloped lower segment is a further technical disadvantage of the direct plan. The tensile strength of the lower segment is influenced by its diameter and the thickness of its wall. Usually the thickness of the wall varies in proportion to the diameter. In some instances the wall is so extremely thin and delicate that the anastomosis is constructed with considerable difficulty. The weak tensile strength

of the lower segment makes advisable in all cases the complete relaxation that is obtained by general anesthesia, so as to permit the segments to be approximated as readily as possible. Otherwise, there is considerable likelihood that the sutures will pull through the wall of the lower segment during the construction of the anastomosis.

The vascular supply of the upper segment has appeared to be adequate in all cases. The blood supply of the lower segment is less well developed, and there may be a question concerning its adequacy in some cases. For this reason the lower segment is freed from the adjacent tissues only for the minimal distance necessary for its transection. A No. 8-F catheter, over which the anastomosis is constructed, is removed after completion of the anastomosis, as the catheter may distend the lower segment, if particularly narrow, and so produce ischemic necrosis.

#### PREOPERATIVE TREATMENT

The extent of the preoperative treatment depends upon the general condition of the patient and the pneumonic complications that may already have occurred. The estimation of the pulmonary status is a matter of immediate concern and should be carried out as soon as the patient is admitted to the hospital. If the infant is cyanotic, mucus should be aspirated from the pharynx and oxygen therapy should be started promptly. During the initial examination, the lung fields will ordinarily show numerous coarse rhonchi resulting from bronchial secretions. The rhonchi will usually disappear after the aspiration of mucus from the pharynx and the hyperventilation of the lungs that is induced by crying or struggling coincident with the aspiration. Aspiration of secretions from the pharynx and upper esophagus should be done at frequent intervals in order to prevent the overflow of secretion into the trachea and to induce hyperventilation so that accumulated secretions in the trachea and bronchi will be effectively expelled.

The pulmonary status is carefully determined by physical and roentgenologic examinations. If a radiopaque solution has not previously been given to establish without doubt the presence of complete esophageal obstruction, it should be used in conjunction with the roentgenologic examination of the chest. The infant is given about 1-2 cc. of iodized oil to swallow. A larger quantity of iodized oil should be avoided as it is likely to be aspirated into the trachea. The position and length of the upper segment are particularly observed during roentgenoscopic examination. The mobility of the upper segment during respiration is considerable and will usually correspond to the distance occupied by the vertical length of two or three dorsal vertebral bodies. In subsequent film studies, the upper segment may appear to occupy a high position merely because the exposure of the film happens to have been made in the expiratory phase of respiration. An apparently high upper segment, therefore, does not preclude the possibility of a satisfactory anastomosis. At the conclusion of the roentgenologic examination, the iodized oil is aspirated from the upper segment by means of a catheter.

The position of the infant is of importance in lessening the possibility of pulmonary complications. From the time that a diagnosis has been made, the patient is placed in the prone position with the foot of the bed elevated. This position favors the drainage of oral secretions to the exterior and lessens the tendency of aspiration of pharyngeal secretions. The position is changed to the alternate lateral positions at frequent intervals to favor drainage from the upper lobes and thereby lessen the tendency for the development of an atelectasis of the upper lobes. If pneumonia or atelectasis has occurred, the use of the alternate lateral positions is continued, but the uninvolved side is kept uppermost for a greater length of time than the involved side. While the involved side is uppermost, the pharynx is aspirated to stimulate coughing and the expulsion of bronchial secretions.

Parenteral fluid consisting of a 3 or 5 per cent solution of dextrose in distilled water is given preferably by the subcutaneous route. The amount of fluid needed to correct dehydration, if present, will necessarily depend upon the extent of the dehydration. The amount needed to maintain the fluid balance should be considerably less than the calculated daily optimal amount for a normal infant of the same weight. Normal saline or Ringer's solution should be avoided because of its sodium chloride content. If pneumonic consolidation has already occurred, sulfonamide therapy should be started by the subcutaneous route. The need for blood or plasma transfusions before operation will depend upon the nutritional level of the infant, as evidenced by the number of days that have elapsed since birth. A blood transfusion is ordinarily not given before operation, and its use is deferred until the time of operation. Ascorbic acid and vitamin K are routinely employed as preoperative measures.

#### INDICATIONS FOR OPERATION

A decision in favor of operation should be made as soon as the infant's general condition is satisfactory. If the lung fields are clear, the sooner the operation is undertaken, the less likely is the chance of a pneumonic complication occurring to a degree sufficient to prevent operation. Usually 6 to 12 hours, and ordinarily not more than 24 hours, will be sufficient time to obtain the maximal beneficial response from the preoperative treatment.

The decision regarding the advisability of operation is made on the basis of several criteria. If infants are premature by more than two or three weeks, it is often questionable whether operation should be performed. The size of the infant is another criterion, in that the larger the infant, the better is the chance that he will withstand the operation. Operation should probably not be undertaken in infants whose birth weight is less than four pounds. Those who are weak and listless, and who have a feeble cry or none at all, are more likely to develop pneumonic complications than strong infants with a good cry. The decision regarding operation in weak infants may need to be deferred until the response to general supportive measures is known. Cyanosis which persists after aspiration of mucus from the throat

and after the use of oxygen therapy is a poor prognostic sign and is regarded at present as a positive contraindication to operation. The body temperature is of importance particularly in respect to dehydration or pneumonia. When fever is present, it is preferable to defer operation until the temperature can be reduced to normal, or nearly normal, by treatment of the causative factor.

The presence or absence of pneumonia is one of the most important criteria regarding the advisability of operation, inasmuch as pneumonia is the chief cause of death in these patients. An extensive bilateral pneumonic consolidation is a definite contraindication to immediate operation. A smaller degree of involvement, particularly if limited to one upper lobe, does not necessarily preclude operation, provided that operation is performed on the side of the pneumonic process. If a barium solution has inadvertently been used for roentgenologic diagnosis and if the barium entered the lungs and produced a pneumonic consolidation, the consolidation is likely to persist. An early stage of pulmonary atelectasis usually responds to corrective measures and does not contraindicate operation, particularly if the operation is performed on the side of the atelectasis. The difficulty is often one of determining whether atelectasis or pneumonia is the predominant pulmonary lesion. Although physical and roentgenologic findings are helpful, the differential diagnosis may depend upon the rapidity of clearing of the lesions or the failure of the abnormal signs to clear by the use of posture, carbon dioxide and oxygen inhalations, and enforced crying or coughing. Other congenital anomalies usually do not contraindicate operation, as the anomalies that are most likely to be encountered are ones that are compatible with life.

#### THE OPERATIVE APPROACH

Ligation of the tracheoesophageal fistula and anastomosis of the esophageal segments can be performed through either a right or left extrapleural approach. In the 24 patients in this series for whom an exploration has been carried out, the left extrapleural approach was used in 12 and the right extrapleural approach in 11. In one patient operated upon early in the series, a right intrapleural approach was used before it was realized that the respiratory embarrassment would be considerably greater with an intrapleural than with an extrapleural approach. In the first cases in this series the left extrapleural approach was found to be satisfactory but in the more recent cases in this series, the right extrapleural approach has been used in preference to the left, because of the greater ease in obtaining the exposure of the lower esophageal segment.

The upper segment is readily exposed from either the right or left side. The presence of the aorta on the left prevents the exposure of the lower segment until the aorta has been mobilized by ligation and division of the upper two or three intercostal arteries arising from it. Forward, downward and mesial retraction of the aorta is then required to maintain exposure of the lower segment. The pressure upon the aorta during its retraction necessarily reduces its lumen and even though the retraction is intermittent,

it is believed that the retraction contributes to operative shock With the right extrapleural approach, the azygos vein is divided and thereafter the exposure of the lower segment is not only better than with the left approach, but it is more easily maintained

As the pulmonary complication plays such an important rôle in the eventual outcome of the case, the side selected for the operation is now chosen according to the preoperative condition of the lungs (Fig 5) If both lungs are clear, the preferred right approach is elected If a pneumonic involvement is present

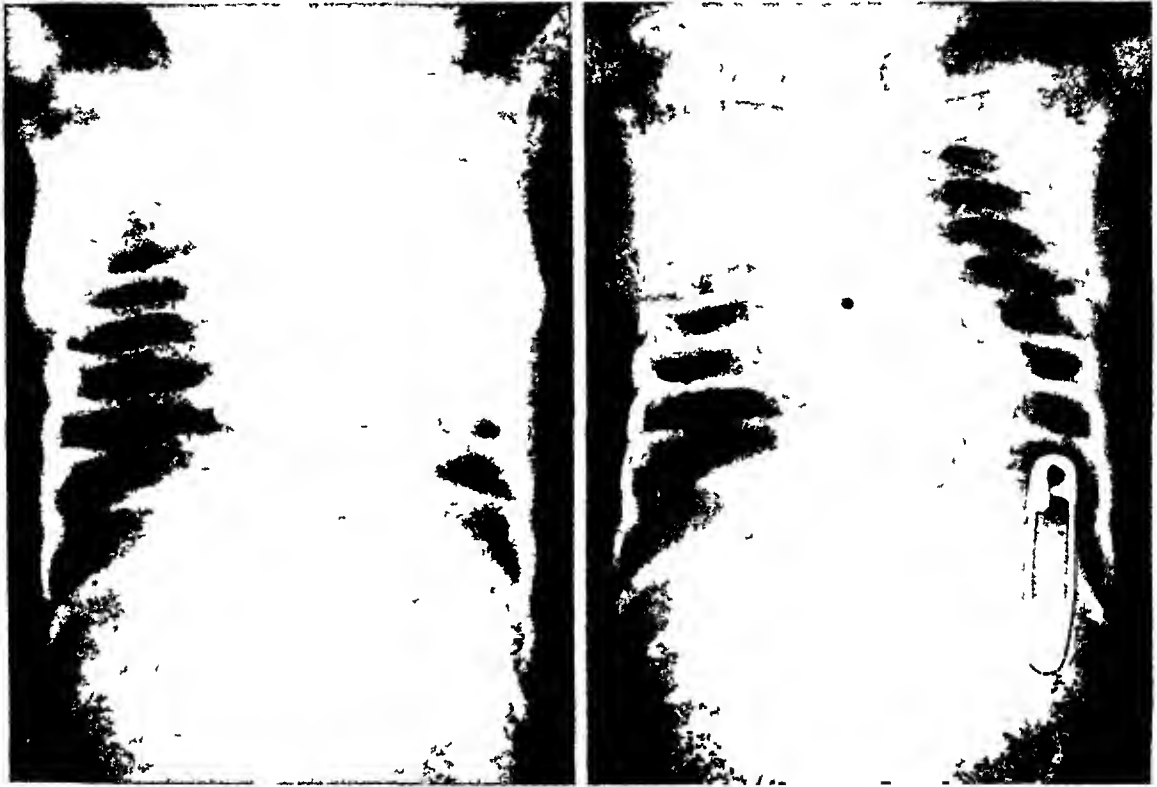


FIG 5—V L, Case 22—(A) Roentgenogram on admission shows small degree of involvement of right upper lobe and extensive involvement of left upper lobe When the patient was turned to the right lateral position during the subsequent physical examination, re-aeration of the left upper lobe occurred, demonstrating that the involvement of the left upper lobe was on the basis of atelectasis and not a pneumonia Roentgenogram (B) was made immediately after the physical examination and three hours after roentgenogram (A) The left upper lobe is now clear The infiltration in the right upper lobe which has persisted in spite of the use of the left lateral position during the physical examination is probably pneumonic in nature Operation was undertaken one hour after roentgenogram (B) The right extrapleural approach was used because of the pulmonary involvement on the right An anastomosis was completed and the patient is now living 13 months after operation

in one lung only, the operation is done from the corresponding side In this way the function of the good contralateral lung will not be impaired by the costal resections and the temporary postoperative extrapleural collapse of the upper portion of the lung The extrapleural collapse of the upper lobe appears at times to have a beneficial rather than a detrimental effect upon a mild pneumonic process within the collapsed upper lobe Also, if the pulmonary involvement is due to atelectasis, improvement of the atelectasis may be expected as the result of the uppermost position of the involved lung during the operation As an upper lobe atelectasis may occur before operation in spite of precautionary measures, the location of the atelectasis can be governed



by the posture of the infant before operation. If during the intervals when the patient is in the lateral position, the left lung is kept uppermost for a longer period than the right lung, the left lung can usually be kept clear. Should an atelectasis develop, it would be likely to occur on the right side and thereby the preferable right-sided approach could be employed.

#### OPERATIVE TECHNIC RIGHT EXTRAPLEURAL APPROACH

The neck is shaved posteriorly up to the external occipital protuberance. The preoperative medication of codeine and atropine is adjusted to the

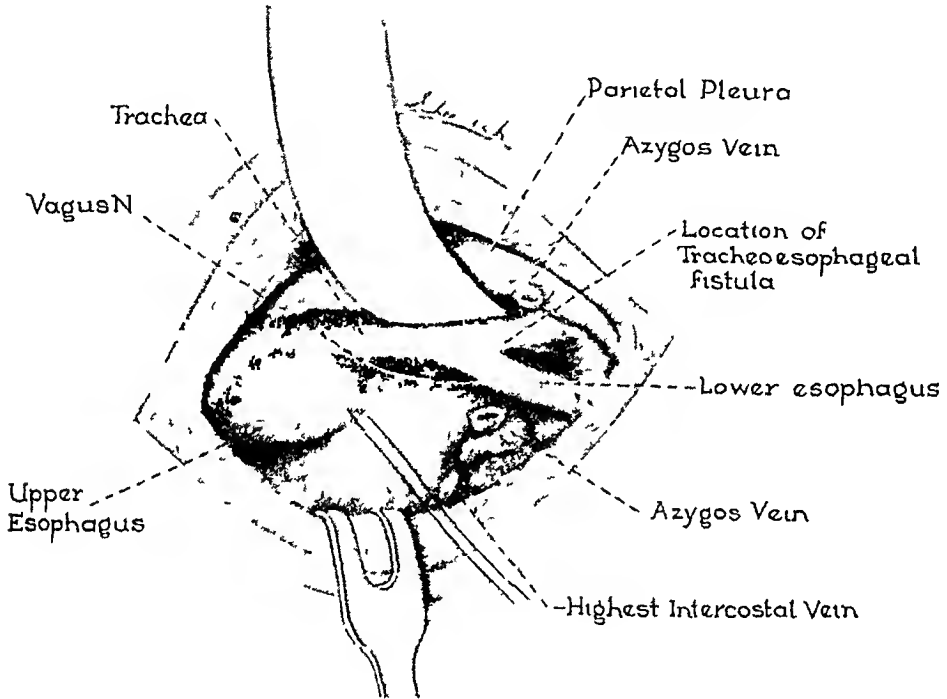


FIG 6—The right extrapleural exposure of the anomaly is illustrated. The posterior portions of the third, fourth and fifth ribs have been resected and the parietal pleura has been freed from the thoracic wall. The azygos vein has been divided in order to expose the lower esophagus. The dilated blind upper segment has been partially freed from the posterior wall of the trachea. The relative size of the upper and lower esophagus, and the usual position of the tracheoesophageal fistula are shown. The right vagus nerve serves as a useful guide for locating the lower segment.

weight of the infant. As a satisfactory means for blood replacement is essential, a cannula is inserted in an ankle vein on the side opposite to the side of the operation. The size of the cannula (Nos 22 F or 24 F) depends upon the size of the vein. Between 100 and 150 cc of whole blood, diluted with an equal amount of physiologic saline or Ringer's solution, is given during the operation and the first several hours after operation. Although the saline or Ringer's solution is undesirable because of its sodium chloride content, a diluent has been employed so that the blood will flow through the small cannula.

The patient is secured to a frame and external heat is applied. After preparation of the skin, the location of the incision is indicated by a cutaneous

scratch before the application of the sterile drapes. Without this precaution, the laxity of the skin may be responsible for an incorrect position of the incision. Local anesthesia consisting of one-half of one per cent procaine solution or one-quarter of one per cent metocaine hydrochloride solution is used until the costal resections are begun. Light ether anesthesia by the drop method is used during the remainder of the operation. An infant-sized face mask for administration of positive pressure oxygen should be available for use in the event that the parietal pleura is inadvertently opened. The incision parallels the lateral border of the sacrospinalis muscle and extends from the second to the sixth ribs, inclusive. Careful hemostasis is essential. The trapezius and rhomboideus major muscles are incised, and the sacrospinalis muscle is retracted mesially. The third, fourth and fifth ribs are resected subperiosteally from the plane of the transverse processes to a point above 1.0-1.5 cm lateral to the angles of the ribs. The third and fourth intercostal nerves and muscles are divided close to the transverse processes, and the corresponding intercostal vessels are doubly ligated and divided. The periosteum of the resected ribs is incised vertically and the extrapleural separation of the parietal pleura is begun. A small periosteal, or dural, elevator allows the extrapleural separation to be done under direct vision. The fibers of the endothoracic fascia hold the pleura tightly to the intercostal muscles between the heads of the ribs. These fibers must be carefully divided under direct vision to prevent the extremely thin parietal pleura from being torn at this stage of the operation. During the further separation of the parietal pleura from the costovertebral gutter, a small gauze pledget, secured in the jaws of a hemostat, is used as a dissector. A spatula retractor is used to hold the parietal pleura out of the costovertebral gutter and to maintain exposure. The arch of the azygos vein is exposed. The parietal pleura immediately beneath it is especially thin and is in particular danger of being punctured or torn. The azygos vein is ligated centrally with two doubled silk ligatures. The main trunk of the azygos vein below the entrance of the highest intercostal vein is singly ligated, the highest intercostal vein is similarly ligated and the azygos vein is divided central to the entrance of the highest intercostal vein. In the earlier cases in this series, an illuminated retractor was employed, but it is cumbersome in the small operative field. The innominate artery may be exposed at times, but if the operative field is limited to the posterior mediastinum, it is usually not visualized.

The areolar tissue posterior to the trachea is infiltrated with a local anesthetic solution to prevent untoward vagal reflexes and the vagus nerve, if seen, is also blocked. The upper esophageal segment is searched for in the loose areolar tissue posterior to the trachea. If the upper segment has a low position, it is usually found without difficulty. If it is not promptly seen, a catheter is introduced into the mouth by the anesthetist and advanced into the upper segment. Gentle pressure upon the catheter pushes the upper segment downward where the tip of the catheter may be felt within the upper segment. The areolar tissue is then freed from the upper segment and a

tension suture is inserted in the blind end. If the upper segment is unusually short, it may be necessary to resect the posterior portion of the second rib and to divide the second intercostal structures in order to obtain adequate exposure of the upper segment.

The lower esophageal segment is usually found without difficulty when it arises at a point between 1 and 1.5 cm above the tracheal bifurcation. If the lower segment is not readily identified, the prominent right vagus nerve can often be seen on the right lateral wall of the trachea or in the space posterior to the trachea. The vagus nerve is traced down to the lower segment, which is then readily found unless it should arise in the crotch between the two main bronchi. Occasionally, a strand of fibrous tissue or muscle extends between the two segments and can be traced downward to the lower segment. Considerable difficulty has been experienced in locating the lower segment when it enters the tracheobronchial tree at an extremely low level, that is, when the lower segment passes directly downward from the carina or one of the stem bronchi. In three of the 24 cases, the posterior aspect of both main bronchi was exposed before the lower segment could be definitely lying in the angle between them. In the two cases with agenesis of the lower esophagus, both main bronchi were exposed posteriorly before the absence of a tracheoesophageal fistula could be definitely determined.

A right-angled hemostat is passed around the lower segment just below its entrance into the trachea or bronchus. A narrow tape or thread is then placed around the lower segment to provide tension and to aid in the freeing of the lower segment up to the fistulous communication. After the lower segment has been freed from the trachea, the decision is made regarding the advisability of attempting an anastomosis. The upper segment is pulled downward with the tension suture and the proximity of the two segments is noted. With the upper segment pulled down, a gap of 0.5 to 1 cm can usually be overcome by the upward mobility of the lower segment after it has been divided. The external diameter of the lower segment should also be estimated. If the lower segment is narrow and its diameter is only three or even four millimeters, the possibility of securing a satisfactory anastomosis is extremely small. If the gap is too great or the lower segment too narrow, the preferable plan, in so far as recovery of the infant is concerned, is to abandon a direct anastomosis and to treat the condition by the indirect method. The lower segment would then be ligated, but not divided so that the factor of possible contamination of the wound would be avoided.

If it seems likely that an anastomosis can be made, the lower segment is ligated with a single or double silk ligature as close as possible to the trachea. A tension suture is placed in the wall of the lower segment distal to the ligature, the lower segment is divided and the mucosa of the two ends is cleansed with a mild antiseptic solution. As a tendency exists for the ligature to roll off the ligated proximal stump, several suture ligatures are used to cover the stump. The lower segment arises from the trachea at a sharp

angle and, as a ligature of the lower segment necessarily lies at a right angle to the direction of the lumen, a several millimeter length of the posterior wall of the lower segment is sacrificed when a ligature is used. If it seems that this additional length posteriorly will be of advantage in the construction of the anastomosis, it can be saved by placing a narrow hemostat across the distal segment almost flush with the trachea and parallel to the direction of the trachea. The lower segment is then divided and the clamp is oversewn with several figure-of-eight plastic silk sutures (Fig 7). Additional interrupted sutures may be used if needed. This method of dividing the lower segment has been used only in the two most recent cases in this series.

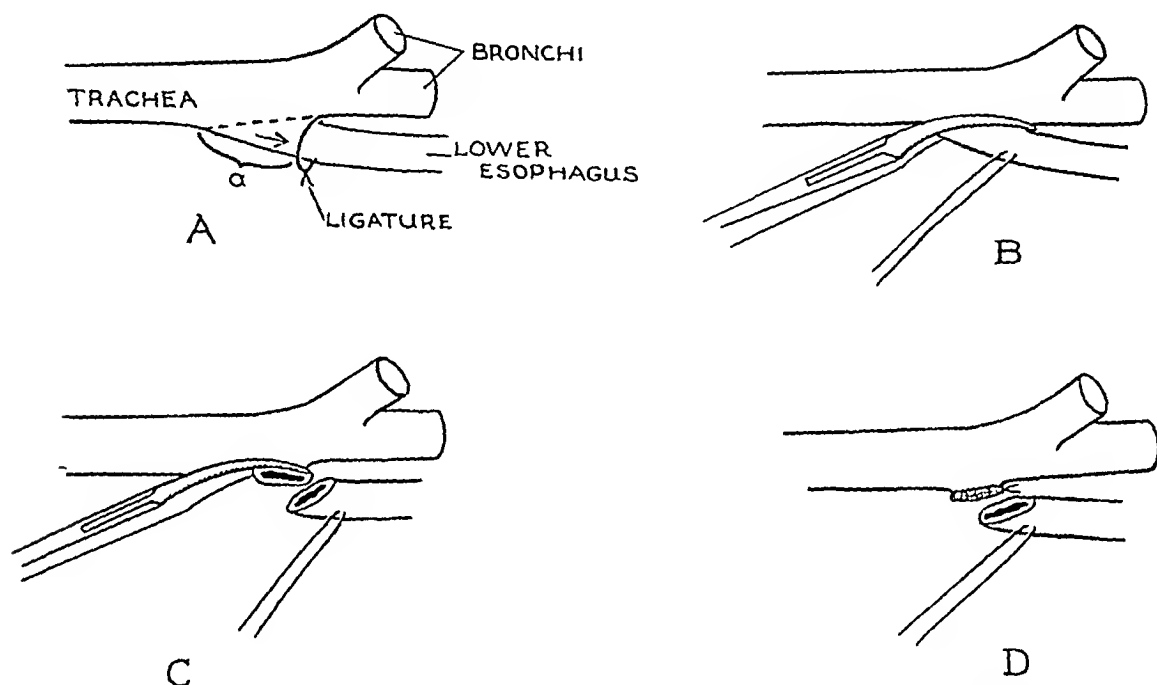


FIG 7—(A) The lower esophageal segment arises from the trachea at a sharp angle. A ligature will, of necessity, lie at a right angle to the long axis of the esophagus. Closure of the fistula by a ligature sacrifices the upper portion of the posterior wall indicated by the bracket (a).

B, C and D illustrate the method of closure of the tracheoesophageal fistula that has been used in the two most recent cases.

(B) The upper portion of the posterior wall of the lower segment is preserved by the placement of a mosquito hemostat across the lower segment at its entrance into the trachea.

(C) The lower segment has been divided by an oblique incision. A greater length of the esophageal wall is preserved posteriorly by this method, and a larger circumference is available for the anastomosis.

(D) The hemostat is oversewn with figure of eight sutures and is removed. Additional interrupted sutures are used to strengthen the closure. By this method the tracheoesophageal fistula is closed by suture, rather than by ligature. The relative efficacy of the two methods in the prevention of re-opening of the fistula has not been established as yet.

The blind end of the upper segment is opened for a distance that corresponds to the diameter of the lower segment. The musculature of the anterior wall of the upper segment is less well developed than it is laterally or posteriorly. As the anterior wall of the upper segment has on occasions split upward during the construction of the anastomosis, the incision in the upper segment carefully avoids the anterior wall. The interior of the upper segment is cleansed with an antiseptic solution. A No 8 F catheter with its flared outer end completely removed is introduced into the two segments by way of the wound. One end of the catheter is advanced into the lower segment until it enters the stomach. The other end is advanced through the upper

segment until it enters the pharynx where the anesthetist grasps it with a hemostat and withdraws the end of the catheter from the mouth. The catheter stabilizes the esophagus during the construction of the anastomosis, and the open ends of the two segments are kept from collapsing, thereby allowing the sutures to be placed more readily than when a catheter is not used.

Considerable difficulty is often encountered in the construction of the anastomosis because of the tension that is present and the thinness of the wall of the lower segment. Delicate, atraumatic round-point needles\* and the

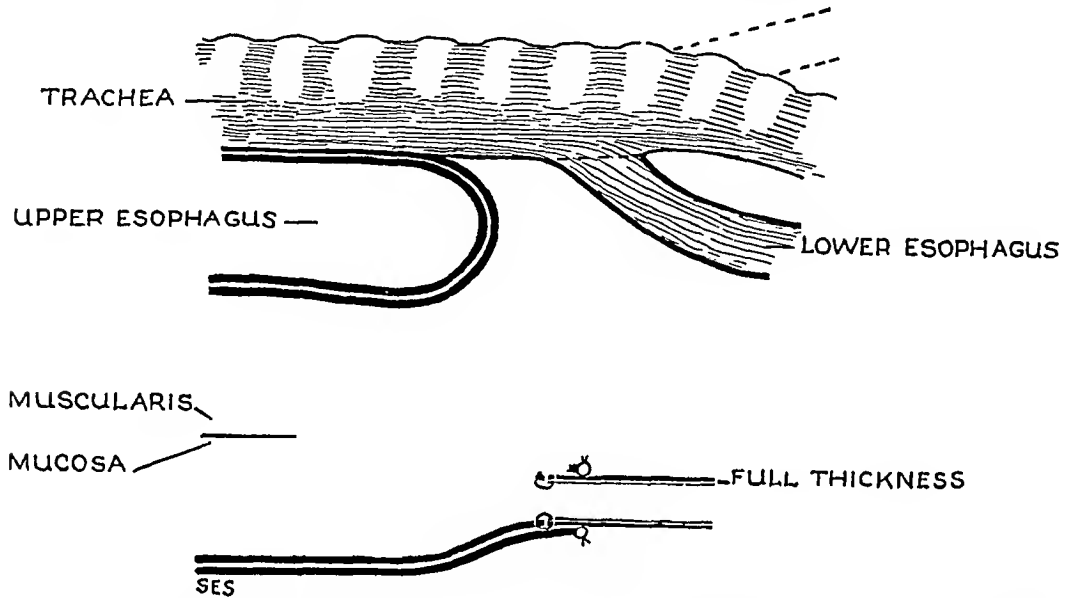


Fig 8—The upper drawing shows the blind upper esophageal segment and the lower esophagus arising from the trachea. The relative size of the two segments and the relative thickness of their walls are illustrated.

The lower drawing shows the completed "telescopic" anastomosis. This type of anastomosis is used because of the discrepancy in the size of the two segments and the discrepancy in the thickness of their walls. The relatively thick wall of the dilated upper segment and the extremely thin wall of the smaller lower segment are illustrated. The thickness of the entire wall of the lower segment is usually no greater than the thickness of the mucosa of the upper segment. The inner row of sutures approximates the full thickness of the wall of the lower segment to the mucosa and submucosa of the upper segment. The outer layer of sutures draws the muscularis of the upper segment downward and anchors it to the outer wall of the lower segment at a level several millimeters below the inner layer of sutures. Interrupted sutures of plastic silk are used in the construction of the anastomosis.

smallest available silk sutures (Deknatel A) are employed, so that a minimal amount of trauma is produced. A "telescopic" type of anastomosis (Fig 8) has been employed for the patients operated upon during the last year and a half. The discrepancy between the thickness of the walls of the two segments readily permits this type of an anastomosis. The thickness of the underdeveloped wall of the lower segment is usually no greater than the thickness of the mucosa of the upper segment. An inner row of about eight interrupted sutures approximates the mucosa and a small amount of submucosa of the upper segment to the full thickness of the wall of the lower segment. As there is considerable mobility of the muscular layer of the upper segment on the submucosa, the muscularis of the upper segment can be pulled downward and sutured to the outer surface of the lower segment, 2 or 3 Mm below the level of the first row of sutures. This second or outer layer of the anastomosis

\* Anchor brand No 1833-4,  $\frac{1}{2}$  circle, taper point

consists of approximately the same number of interrupted sutures that are used for the inner layer. The catheter is withdrawn after the anastomosis is completed.

A pneumothorax resulting from the accidental opening of the pleura during the operation is not well tolerated because of the normally low respiratory reserve of infants. If a pneumothorax should occur, the lung should be promptly reexpanded with positive pressure oxygen administered by a face mask, and the opening through the pleura should be closed if possible. The thin parietal pleura, however, does not lend itself well to suturing, as the puncture wounds caused by the smallest available needle may allow leakage of air or cause a further tear of the pleura. After the parietal pleura has been freed from the thoracic wall, the redundancy of the pleura often allows the torn edges to be grasped and pulled outward. If the tear is not too large, an encircling ligature can be placed beyond the tear, and an air-tight closure is thereby obtained. This maneuver usually can not be employed if the tear is in the region of the arch of the azygos vein. When the tear can not be closed, a small gauze pack is placed against the pleural opening after the lung has been expanded by positive pressure oxygen. Air can be prevented from entering the pleural space by maintaining firm pressure against the pack with the spatula retractor. At the time of closure of the thoracic wall incision, the inner portion of a small gauze drain is placed against the opening in the pleura. Expansion of the lung is maintained by the positive pressure until the wound is closed air-tightly around the drain. The pressure exerted by the gauze keeps the parietal pleura in contact with the lung, and the irritation produced by the gauze causes a rapid adherence of the lung to the parietal pleura at the site of the tear. This method of sealing the opening in the parietal pleura has been successful in the prevention of an empyema, even though the extrapleural wound in some of the cases has become grossly infected as a result of leakage of the anastomosis.

The wound is irrigated with physiologic saline solution before the closure is begun. In the event that the pleura has not been opened, a soft rubber tissue drain is placed near the site of the anastomosis as a safeguard in the event that leakage of the anastomosis should occur. The long free anterior ends of the divided intercostal muscles are sutured to the under surface of the sacrospinalis muscle, and the extracostal wound is closed in layers with interrupted sutures. Fine catgut is used for the buried sutures because of possible suppuration of the wound resulting from leakage of the anastomosis. The skin edges are approximated with interrupted sutures of plastic silk.

The operative technic for the left extrapleural approach<sup>5</sup> varies only in the exposure of the anomaly. After the parietal pleura has been separated from the thoracic wall, the highest intercostal vein is doubly ligated and divided. The left subclavian artery is identified and retracted forward, so as to expose the retrotracheal space. The upper segment of the esophagus is located by the same measures described for the right extrapleural approach. In order to expose the lower esophageal segment, the uppermost two or

three intercostal arteries are doubly ligated and divided close to the aorta. The aorta is then retracted forward, downward and mesially. The left vagus nerve is not seen, but the left recurrent laryngeal nerve may be encountered and injury to it should be avoided.

#### POSTOPERATIVE MANAGEMENT

If physical or roentgenographic signs of a moderate or considerable pneumothorax are present, the air is aspirated from the pleural space. The infant is placed upon the operated side to reduce the paradoxical motion of the thoracic wall resulting from the costal resections. The foot of the bed is elevated to favor the drainage of secretions from the respiratory tract to the exterior. External heat is applied and oxygen is administered continuously with a face mask while the patient is being returned to the nursery. Prior to the use of oxygen during this interval, intense cyanosis often was present upon the patient's return to the nursery. Oxygen is subsequently administered by means of a tent. The rectal temperature is recorded and, as the temperature is frequently subnormal, external heat is continued. The temperature of the air within the tent is maintained at a considerably higher level than is customary with oxygen tents. If the infant is premature, or if difficulty should be experienced in maintaining the body temperature at a normal level, the patient is placed in an incubator. The intravenous infusion is slowly continued until the required amount of 100 to 150 cc of blood has been given.

The condition of a few of the infants during the first several hours after operation has been precarious. Sudden attacks of cyanosis with complete cessation of respiration have occurred as a result of obstruction of the airway by secretions. Immediate aspiration of the pharynx is required and, artificial respirations, carbon dioxide and oxygen inhalations, and subcutaneous injection of caffeine sodium benzoate are used to restore respiration. The recovery of the infant from these episodes is almost as sudden and dramatic as is the speed with which they arise. Should the onset of these episodes not be recognized promptly, death may occur suddenly before corrective measures can be instituted. To prevent these attacks insofar as possible, the character of the respirations is carefully determined at frequent intervals, and pharyngeal suction is used at the first appearance of a wet-type of breathing.

Subcutaneous fluid, consisting of a 3 or 5 per cent solution of dextrose in distilled water, is given during the first 12 or 18 hours after operation only if an insufficient amount of fluid has been administered in conjunction with the blood transfusion. The subcutaneous daily amount of subcutaneous fluid is restricted, because of the danger of producing pulmonary edema by the administration of too large a quantity. The amount of fluid ordinarily given is about one and one-half ounces per pound of body weight, instead of the customary two and one-half ounces per pound. The subcutaneous fluids consist of a 3 or 5 per cent solution of dextrose, supplemented with the

# ATRESIA OF ESOPHAGUS



FIG 9—S S, Case 19—(A) Portable roentgenogram after ingestion of iodized oil five days after left extrapleural ligation of tracheoesophageal fistula and primary anastomosis of esophageal segments. Leakage of the anastomosis did not occur. The upper esophagus is dilated and the lumen at the site of the anastomosis is narrow. All feedings were continued by mouth. Gastrostomy and esophageal dilatation were not necessary.

(B) Roentgenogram 9.5 months after operation. Spontaneous enlargement of the esophageal lumen has occurred at the site of the anastomosis. The upper esophagus is not dilated. In subsequent roentgenologic studies (not illustrated) iodized oil passed through the esophagus so rapidly that satisfactory roentgenograms were not obtained. A slight narrowing was evident at the site of the anastomosis.

(C) Photographs of patient one year after operation show the scar of the healed left extrapleural operation. A gastrostomy has not been necessary.



desired amount of a 0.5 per cent solution of sulfadiazine. Physiologic saline solution is not used, except for the minimal amount required in conjunction with blood transfusions. The onset of edema of the extremities is an indication for a transfusion of whole blood. Blood is used in preference to plasma, as the possibility of producing pulmonary edema appears to be greater when plasma is employed. One of the early cases in this series died from pulmonary edema resulting from the administration of an excessive amount of physiologic saline solution, and a more recent patient died from pulmonary edema following a plasma transfusion.

A portable roentgenogram of the chest is made daily during the first several days after operation. The infant is placed in a sitting position during the exposure of the film. If residual air is present within the pleural space, the indication for withdrawal of the air will depend upon the amount that is present. A moderate amount should be removed, a small amount should probably be allowed to remain because of the danger of injury of the lung with the aspirating needle.

The rubber or gauze drain is shortened on the first or second postoperative day and it is removed completely on about the fourth day. After removal of the drain, the drainage track is packed daily with a narrow gauze strip to allow the wound to heal satisfactorily by second intention. A portable roentgenogram is made on the second day after the administration of one or two cubic centimeters of iodized oil by mouth. If leakage of the anastomosis is not evident, fluids in very small amounts are started by mouth. Ordinarily only one or two cubic centimeters of a 5 per cent dextrose solution are given at hourly or two hourly intervals. If the infant tolerates this amount of fluid without difficulty, the amount is gradually increased on the following day. On the fourth postoperative day, iodized oil is again given by mouth and, if leakage is not apparent in the roentgenograms, a small amount of a formula, diluted with an equal amount of 5 per cent dextrose, is begun. If the formula does not produce choking and if leakage does not subsequently occur, the amount of the formula is gradually increased until the eighth or tenth day when one, or one and one-half ounces will usually be taken at three-hourly intervals. During this period supplementary 3 or 5 per cent dextrose solution is given daily by subcutaneous infusion and at times by rectal instillation. Supportive blood transfusions are given every second or third day. In this way the infants can be tided over the critical period of an insufficient fluid and caloric intake by mouth. Four of the six living patients in this series did not develop an external esophageal fistula, in three of the patients the above plan was used satisfactorily and a gastrostomy was not needed. In the fourth patient a gastrostomy was required because of a recurrence of a tracheoesophageal fistula.

As soon as the infant's condition permits, a roentgenoscopic examination of the reconstructed esophagus is done. Iodized oil is again used and its progress through the esophagus is observed. During the first few weeks after operation, a delay in the passage of oil is present at the site of the

anastomosis, even though a definite stricture may not be present. The narrowness of the lumen at the level of the anastomosis and of the esophagus below the anastomosis apparently accounts for the delay, inasmuch as spontaneous enlargement of the lumen and a more rapid passage of the opaque medium occur during the succeeding weeks (Fig 9). Later, the passage of the iodized oil has been so rapid in several cases that it has been necessary to use a thick barium paste in order to obtain satisfactory roentgenograms. The roentgenoscopic examination is repeated at intervals, however, in order to ascertain whether a stricture is developing.

When an external esophageal fistula develops as a result of leakage of the anastomosis, a gastrostomy is required for feeding. A gastrostomy, however, subjects the patient to increased risks and it has been an important cause of death in those patients who have required it. One infant died ten hours after the gastrostomy, and no cause of death could be determined other than the fact that the infant had been subjected to an additional operation and had not had a transfusion in conjunction with the gastrostomy. Three infants died of hemorrhage from the region of the gastrostomy. The hemorrhage in one case occurred from ulceration of the umbilical vein and in another instance it resulted from ulceration of the gastric wall in the region of the gastrostomy tube. The third patient died four months after the gastrostomy operation from malnutrition resulting from leakage around the tube and from a terminal hemorrhage from the stomach. Leakage of the oral feedings around the gastrostomy tube and prolapse of the gastric wall adjacent to the gastrostomy are present in one of the living patients. In this case a plastic closure of the gastrostomy will be needed, but this operation has not yet been undertaken because a continuous thread is being kept in place for retrograde dilatation of an esophageal stricture. In the past a Stamm-type of gastrostomy has been used and the catheter has been brought out through the incision. In the last patient in this series, operated upon by Dr. John Alexander, the catheter was brought out through a stab incision. This plan appears preferable because of the thin abdominal wall in infants and the tendency for local disruption of the wound around the catheter when the latter is brought through the main incision. A Witzel-type of gastrostomy is recommended by Ladd and Gross as a satisfactory type of gastrostomy for infants.

Spontaneous healing of an external esophageal fistula occurred in the three patients who survived this complication, but the development of a partial stricture accompanied the process of healing (Cases 10, 22 and 23). In Case 23 a complete stricture occurred after the primary operation, and a partial stricture occurred after correction of the stricture at a secondary operation. As the extent of the stricture can not be determined in advance, the infants who develop an external esophageal fistula should be given a fine silk thread to swallow as soon as the thread can be recovered safely from the stomach by way of the gastrostomy opening. The thread is kept in place for subsequent retrograde dilatations in the event that they are necessary.

A leakage of the anastomosis with a resultant external esophageal fistula is a serious complication with regard to the feeding of the infant. The feedings are given through the gastrostomy tube, but the normal tendency of an infant to regurgitate gastric feedings into the esophagus results in the loss of more or less of the feedings through the external fistula. The gastrostomy feedings will, in such patients, need to be given in smaller amounts and at more frequent intervals than would otherwise be the case, in order to reduce the tendency to regurgitation. In three patients this plan was successful in the prevention of any significant loss of the feedings. In three other patients this plan was not successful and the resulting malnutrition was the chief cause of death. In one of these cases unsuccessful attempts were made to insert a catheter through the track of the gastostomy opening and into the duodenum for the purpose of instituting duodenal feedings. On repeated attempts, the catheter could be guided into the pylorus but it could not be made to enter the duodenum. This maneuver was possible, however, in another patient who developed malnutrition from leakage around the gastrostomy tube, but the patient died before the malnutrition could be corrected. The use of a jejunostomy rather than a gastrostomy has been considered, but has not been employed in the cases in this series. A jejunostomy would not permit retrograde dilatations although it could be used to provide adequate nourishment until the external esophageal fistula had had an opportunity to close.

#### RESULTS

A reconstruction of esophageal continuity for congenital atresia is an extensive operation for a new-born infant, even when the circumstances pertaining to the operation are entirely favorable. The ability of the infant to withstand an exploratory operation will be influenced largely by its size and general condition on admission. The possibility of restoring esophageal continuity will depend upon the nature of the anatomic findings. As these factors are uncontrollable, they will prevent the operation from being attempted in some cases and in other cases, they will prevent an anastomosis from being completed. In this series of cases, the poor general condition of the patient prevented operation from being undertaken in four, or 14.3 per cent, of the 28 patients who have been seen during the period that the operation of primary anastomosis has been employed. An anastomosis was found to be possible in 17, or 70.8 per cent, of the 24 patients for whom an exploration of the anomaly was performed, and an anastomosis was made in 16, or 66.7 per cent, of the 24 patients.

The details of operative technic and preoperative and postoperative care are factors which are controllable. As an improvement in the management of these cases can be expected, the results in subsequent cases should be superior to those obtained to date during the initial experiences with this operation. In this series of cases, an increase in the recovery rate of the patients for whom an anastomosis was possible occurred with increasing experiences (Table I).

ATRESIA OF ESOPHAGUS

The improved results in the past year have been due to several factors. The use of larger blood transfusions in the replacement of operative blood loss and the use of only the minimal amount of physiologic saline solution that has been necessary in conjunction with the blood transfusions have resulted in a striking decrease in the incidence of postoperative edema, whereas in the earlier cases, edema occurred in all patients who survived the operation for a period of over two days. The difficulty of securing an anastomosis without subsequent leakage has been partially overcome by the

TABLE I  
CONGENITAL ATRESIA OF THE ESOPHAGUS  
RESULTS IN 28 PATIENTS DURING PERIOD OF USE OF THE OPERATION OF PRIMARY ANASTOMOSIS

	1939	1940	1941	1942	1943	Total
Number of patients	2	2	4	6	14	4
No operation—poor general condition	—	—	1	1	2	8
Anastomosis not possible	—	2*	—	2	4	8*
Anastomosis	2	—	3	3	8	16
Living	—	—	1	1	4	6
Per cent of operative recoveries following anastomosis	0%	0%	33%	33%	50%	37.5%

\* One patient (1940) presented ideal anatomic indications for anastomosis, but anastomosis was not attempted.

Four patients admitted 1935-1938 (before use of anastomosis)

Three treated by gastrostomy—Died  
One—no operation —Died

use of the telescopic type of anastomosis. The complications arising from pleural perforation that can not be closed have been obviated in the recent cases by the placing of a small gauze pack against the pleural opening during the operation and at the conclusion of the operation.

An analysis of the causes of death shows that pneumonia occurred in most of the fatal cases. Fat stains of the lungs were used in the cases having autopsies and in several of them a lipid pneumonia was found. Atelectasis of the fetal or acquired type was found in five cases in which pneumonia was not present at autopsy examination. Acute pulmonary abscesses were noted in one case. The pulmonary complications have often been accompanied by other complications that have been more important in the cause of death. The other complicating factors have included operative shock and insufficient blood replacement, malnutrition resulting from loss of gastrostomy feedings, sepsis from infection of the operative wound, pulmonary edema from excessive amounts of physiologic saline in one case and from a reaction to a plasma transfusion in another case, hemorrhage from the site of the gastrostomy and hemorrhage from the distal esophagus. Table II summarizes the findings and results in all cases of congenital atresia of the esophagus admitted to the University of Michigan Hospital prior to April 1, 1944.

Six, or 37.5 per cent, of the 16 patients for whom an anastomosis was done are living from seven months to three years and one month after operation. The reconstructed esophagus is patent in all instances. The oldest patient (Case 10) has been reported in detail in a previous communication.<sup>5</sup> This case is the first successful one of reconstruction of the esophagus by



C

B

A

FIG 10.—J M, Case 10.—(A) Preoperative roentgenogram showing the dilated blind upper esophagus and the presence of air in the stomach and intestines

(B) and (C) Roentgenograms following ingestion of sugar four months after operation. The upper portion of the esophagus is moderately dilated, and a short narrow stricture is present at the site of the anastomosis. Leakage of the anastomosis occurred during the second and third weeks after operation, but the external esophageal fistula has healed (Haight and Towsley.<sup>5</sup> By permission of Surgery, Gynecology and Obstetrics)

extrapleural ligation of the fistula and primary anastomosis. The patient has developed normally and her weight at the age of three years was 29 pounds. The diet of this patient is not unusual except for the fact that ground meats and sieved vegetables are used instead of coarser foods. In this case a stricture developed subsequent to leakage of the anastomosis, but serial roentgenographic examinations have shown a gradual increase in the size of the lumen at the site of the stricture (Figs 10 and 11). The stricture was dilated once by Dr J. H. Maxwell when the patient was 17 months of age. During the first two years after operation, the patient was troubled considerably by accumulations of mucus in her throat but this symptom has greatly lessened during the last year.



FIG 11—J. M., Case 10—Roentgenograms three years after operation. Progressive enlargement of the lumen of the esophagus has occurred at the site of the anastomosis. (Courtesy of Dr M. Cooperstock, Northern Michigan Children's Clinic, Marquette, Michigan.)

The next oldest patient (Case 18) is 19 5 months of age. In this case a soft rubber drain, that was introduced into the extrapleural space at the conclusion of the operation, was unintentionally removed on the first post-operative day. The external wound healed *per primum*, but a fistula developed between the esophagus and the trachea as a result of a small leak at the anastomosis and a reopening of the original tracheoesophageal fistula. The lumen of the esophagus remained patent. Gastrostomy feedings were employed for a period of 16 months. The fistula gradually became smaller and it closed spontaneously 14 months after operation. All feedings have been given by mouth for the past two months and the gastrostomy wound is being allowed to close. A bilateral pneumonitis that is present apparently began as a result of secretions within the esophagus having gained entrance into the trachea when

the recurrent tracheoesophageal fistula was still open. The patient's weight is now 16 5 pounds \*

The third oldest patient (Case 19) is now living 14 5 months after operation. In this case the two esophageal segments were smaller than usual, and the lower segment entered the trachea immediately above the bifurcation. This patient's postoperative convalescence was exceptionally satisfactory. Leakage of the anastomosis did not occur, and a gastrostomy was not needed. The patient is able to swallow all foods customarily given to a child of this age, and the present weight is 19 pounds.

In the fourth living patient (Case 22) the anastomosis was less satisfactory than usual, as the anterior wall of the upper segment split in an upward direction during the construction of the anastomosis. A second row of sutures could be used around only half of the circumference of the anastomosis. A large external esophageal fistula developed three days after operation and a gastrostomy was done three days later. The external fistula closed spontaneously six weeks after operation. A very tight stricture developed and feedings by gastrostomy were used for nine months. A thread was subsequently swallowed and is now being used for retrograde dilatations. The patient is now 13 months of age. For the past three months, the feedings consisting of cereals and liquids have been taken entirely by mouth. The gastrostomy opening is unsatisfactory because of its large size and a prolapse of gastric mucosa. The gastrostomy is slowly becoming smaller with the use of a constant pressure dressing over the opening. The weight has increased four pounds during the past month and at present the patient weighs 14 pounds.

The fifth patient (Case 26) (Figs 12, 13 and 14) is living 10 months after operation. A gap of three centimeters existed between the two segments before the anastomosis was made. Although there was roentgenographic evidence of a small leak at the site of the anastomosis from the fifth to tenth day, an external esophageal fistula did not develop. Feedings by mouth were continued during this interval and a gastrostomy was not necessary. The extrapleural wound was completely healed 10 days after operation, and the patient was discharged from the hospital 35 days after operation. The infant has developed normally and was in excellent condition when last seen at the age of six months \*

The sixth and most recent living case (Case 30), is now seven months

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\* Condition on August 10, 1944, of

1 Case 18. A more recent roentgenologic examination of the esophagus with iodized oil reveals a persistence of the tracheoesophageal fistula. Gastrostomy feedings have been resumed and a plastic closure of the fistula will be required.

2 Case 26. This patient was examined at the age of one year. His general condition continued to be excellent and he experienced no difficulty in swallowing.

3 Case 30. Feedings have been given orally for the past 15 months. The wheezing during feedings has largely subsided. The attacks of apnea and respiratory arrest have almost disappeared, only one attack having occurred during the past two months. Esophagoscopy shows no evident abnormality of the reconstructed esophagus.



FIG 12—(A) and (B) Roentgenograms after ingestion of iodized oil show the upper esophageal segment to be smaller than usual. Air is present in the stomach, demonstrating the presence of a tracheoesophageal fistula. Congenital dextrocardia.

(C) Portable lateral roentgenogram two days following right extrapleural ligation of fistula and primary anastomosis. The iodized oil demonstrates the esophagus to be patent, although the lumen is narrow at the site of the anastomosis. A small, temporary extravasation of oil was noted on roentgenograms (not illustrated) on the fifth and tenth postoperative days, but an external fistula did not occur. Feedings by mouth were continued and a gastrostomy was not done.



old The patient has not been discharged from the hospital because respiratory difficulties occur with oral and gavage feedings In this case the anastomosis healed without the development of an external fistula, although a very small temporary leakage of the anastomosis was seen in the roentgeno-



FIG 13—F B, Case 26—(A and B) Roentgenograms, six months after operation show the lumen of the esophagus to have enlarged There was no delay in the passage of rugar through the esophagus



FIG 14—F B, Case 26—(A and B) Photographs of patient one month after operation The healed right parascapular incision is seen A gastrostomy has not been needed  
(C) Photograph of patient six months after operation

grams Roentgenoscopic examination shows only a slight delay in the passage of lipiodol through the region of the anastomosis, and a No 18 F catheter can be easily introduced into the stomach Wheezing occurs during all feedings, but it is more severe during oral feedings The respiratory

difficulty is characterized by apnea, cyanosis and respiratory arrest which occasionally occur shortly after the conclusion of a feeding, whether it be by the oral route or by gavage. Immediate resuscitative measures are needed to restore respirations. As the gavage feedings provoke the symptoms less often than do the oral feedings, the gavage feedings have been used almost exclusively and are being continued. The explanation for the respiratory attacks is not clear. A recurrence of the tracheoesophageal fistula has been considered as a possible cause for the symptoms, but the roentgen examinations reveal no evidence of a fistula. A faulty mechanism of deglutition has also been considered as a possible cause, although the epiglottis appears to be normal on laryngoscopic examination\*.

#### SUMMARY

The anatomic and surgical problems concerned with the correction of congenital atresia of the esophagus with tracheoesophageal fistula are presented. Reconstruction of esophageal continuity by a single-stage operation consisting of an extrapleural closure of the tracheoesophageal fistula and an anastomosis of the esophageal segments offers the most satisfactory approach to the correction of the anomaly. A primary anastomosis of the upper and lower esophageal segments was done in 16 of the 24 patients for whom an exploration of the anomaly was undertaken. Six, or 37.5 per cent, of the 16 patients for whom an anastomosis was performed are living from seven months to three years and one month after operation, and the reconstructed esophagus is patent in all instances.

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DISCUSSION—DR WILLIAM E LADD, Boston Doctor Haight justly remarks that congenital atresia of the esophagus has proven amenable to surgical correction only in very recent years As far as I know, Doctor Leven, of St Paul, has the oldest living patient, and my oldest living patient is 24 hours younger than his They are both now over four and one-half years old

Doctor Haight is certainly to be congratulated on his presentation of the subject and on his splendid results He has made a real contribution to this baffling problem I am in complete sympathy with his idea that extrapleural ligation of the fistula with primary anastomosis is the operation of choice when feasible The feasibility of the plan depends on the findings in the individual case, and on the surgeon's ability The high percentage of cases that Doctor Haight considers feasible for primary anastomosis makes it unnecessary to comment on his ability

At The Children's Hospital we have had the comparatively large series of 72 cases Up until 1939 the experience was valuable largely for furnishing pathologic material, and for teaching us what not to do Since that time, however, there has been a rift in the clouds, and we now have 11 living patients During the past year we have operated upon 13 patients, of whom eight are living In five of these patients a primary anastomosis was attempted, and two are living In the other eight patients the fistula was tied off, an esophagostomy and gastrostomy performed, and six of these eight patients are living Two of this latter group were a little premature, weighing 4 pounds 6 ounces and 4 pounds 8 ounces, respectively In our oldest patient, now 45 years old, the anterior esophagus is continuing to function satisfactorily

I believe there always will be some patients in whom a primary anastomosis will not be feasible We have had at least two patients in whom the lower segment of the esophagus extended not over a half inch above the diaphragm and the upper segment was not below the second or third dorsal vertebra One of these patients is among our group of living cases

From data at hand to date, it would seem that the multiple-stage operation is a considerably safer procedure, though in some ways less desirable The advantages of primary anastomosis make this operation preferable in patients in whom the two segments are close together

## ATRESIA OF ESOPHAGUS

I would like to show some slides demonstrating the technic we have used for both the primary anastomosis and the multiple operations

(Slide No 1) Type 1 is less amenable, Type 2 is the rarest, Types 3 and 4 are the most common, and Type 4, in which the fistula enters the trachea not above the bifurcation but in the carina, appears to be the most common in the last two years. Prior to this time, Type 3 had been the most common. Type 5 is again, rare, and it is only a very short embryonic step from Type 5 to the type in which there is no atresia, and just a tracheoesophageal fistula.

(Slide No 2) The approach is always made on the right side for the reason that it is easier, due to the fact that there are fewer important anatomic structures in the way. A curved incision is made between the scapula and the spine, and the scapula is retracted laterally. A rather long section of the fourth rib is resected, and the third and fifth ribs are cut. Then the pleura is pushed forward, the azygos vein is resected, and the lower portion of the esophagus identified. In the early cases we simply ligated the tracheo-esophageal fistula. In the later cases we have not only ligated but also cut the tracheo-esophageal fistula, turning in both ends. The next slide will show the reason for this change in technic.

(Slide No 3) This is a child that had done extremely well for more than three weeks, and was a very disappointing result. At the end of three weeks, following a gastrostomy feeding, the child suddenly aspirated all the gastric contents and drowned. You can see there is a little black stitch that had cut through all the muscular coats of the esophagus, the esophagus had recanalized, and the gastric contents went back into the lungs and drowned this child. We had that happen in one other case, but, fortunately, we recognized that it was happening. The contents of the stomach were evacuated and we reoperated and cut off the fistula, and that child is still living.

(Slide No 4) Now, in the cases in which a primary anastomosis cannot be done we have reconstructed an anterior esophagus in this manner. A rope is made in the right axillary line first, and where the rope is taken from, a Thiersch graft is placed, in order not to pull over the skin of the chest wall. The lower end of the rope graft is now freed and attached over the esophagostomy opening. The next step consists of making a skin-lined tube from the esophagostomy opening down close to the gastrostomy opening. The rope graft is then used, as you might say, to make the roof of the new esophagus.

(Slide No 5) This shows the method of attachment of the end of the rope graft, which I think is moderately important and self-explanatory.

(Slide No 6) After the epithelial-lined tube and skin-covered tube have been completed from the esophagostomy close to the gastrostomy, another tube graft is constructed from the left side, and practically the same procedure is followed to unite the two and complete the anterior thoracic esophagus.

(Slide No 7) In one case we pulled the lower segment of the esophagus down through the diaphragm and brought that up on the anterior chest wall. This case is still living, but I have had a great deal of trouble with it, because of a fistula which has developed between that and the epithelial-lined tube. It is now healed, and I hope the result is going to be satisfactory, but it has given a great deal of trouble, and I do not think I would do it again.

(Slide No 8) Early cases of primary anastomosis died with leakage, but since we have adopted this method of suture we have not had any leaks.

In the top left hand corner the slide shows how we insert first in the upper segment small over-and-over stitches to act as stays, which give a long purchase so that the sutures will not pull out. The same thing is done in the lower segment, and the two segments are approximated. Three or four stitches are placed, anastomosing the mucous membrane first. Then the first stay-sutures are all tied, and two or three uninterrupted Connell sutures are placed to turn in the outer part of the layers of the esophagus.

We have done that over a catheter and left the catheter in. I think very likely Doctor Haight's idea of pulling the catheter out as soon as the anastomosis is completed, may be a better procedure.

(Slide No 9) This is our oldest child, 4 1/2 years of age. She eats quite a liberal diet. I tried to obtain a roentgenogram showing the outline of the esophagus, but the barium goes down very fast, and it is very difficult to obtain a satisfactory film.

It is a mistake to think that food stays in the skin tube—it goes through very rapidly. Apparently there is plenty of peristalsis in the upper segment of the esophagus to push anything down into the stomach, and very quickly.

(Slide No 10) This is the oldest child in whom we have performed a primary anastomosis, now nine months old, and weighing about 17 pounds, she is a good, fat, healthy, well-nourished child, as you see by the picture.

Again, I want to congratulate Doctor Haight on his primary anastomosis, and I think he has really made a great contribution to this difficult problem.

DR N LOGAN LEVEN, St Paul, Minn. I also wish to congratulate Doctor Haight. My experience parallels that of Doctor Ladd, but is not as extensive.

Since 1939, I have operated on these cases, doing an extrapleural ligation, and have five that are surviving. The oldest is over four and a half years and the youngest is about three months.

I feel that this operation of extrapleural ligation will always be necessary in some cases, as in the one-third of cases that Doctor Haight pointed out. I believe that in premature children that weigh four pounds, or under, it is exceedingly difficult to perform an anastomosis. My experience is not extensive in that regard. I have operated upon only two, doing primary anastomoses, and neither of them survived. One weighed about 1,900 Gm.

In one case in which I did an extrapleural ligation the upper pouch ended at the suprasternal notch, and when it was brought out the lower end was well above the clavicle. In this case an anastomosis would have been impossible.

I believe that the operation of extrapleural ligation is simpler and safer, but it certainly entails considerable subsequent surgery to complete the case.

DR ROLLIN A DANIEL (Vanderbilt Hospital, Nashville, Tenn.) I want to add my congratulations to those of the others for this very fine piece of work which Doctor Haight has accomplished.

We, at Vanderbilt, have operated upon seven patients with this condition during the last two and a half years, all of whom had tracheo-esophageal fistulae of the type described by Doctor Haight as being the most common. In six of these instances the fistula has been exposed and extrapleural ligation has been carried out. In the first four, however, exteriorization operations were performed, while in the last three, attempts were made to effect an end-to-end anastomosis of the esophagus. This was successful or was accomplished, in two patients, and one of these patients is still living at the age of five months. This child did get a stricture which is still being dilated through a gastrostomy.

We have come to feel that the following points are of some importance:

First, that operation should not be delayed for very long, only long enough to correct fluid deficiencies and to administer plasma, as may be thought necessary.

Second, that general anesthesia probably should not be employed, but that the operation should be carried out with local anesthesia in the skin or no anesthesia at all.

Third, that the extrapleural approach is the proper one, and that it should be carried out on the right side, although in the one successful case which we have to date, the operation was performed from the left side.

DR CAMERON HAIGHT (closing) I appreciate very much the discussion on this subject, because it allows an opportunity to survey the results that have been accomplished to date. Doctor Donovan had planned to be here today to mention the results at the Babies Hospital, where Doctor Humphreys has three patients who have survived the multiple-stage procedure, one patient who is living eight months following a primary anastomosis, and another patient who is living several days following an anastomosis. Including these cases, and those mentioned in the text of the paper, and by the discussers, there are 30 living patients, although recent follow-up information is not available on two of the patients (Shaw, Nettrour), referred to in the text. It is very gratifying, therefore, to see that definite progress has been made in the treatment of a condition which, up to five years ago, had not been successfully corrected by surgery.

In several of our cases we endeavored to obtain intrathoracic esophageal continuity, rather than electing the multiple-stage principle, when the anatomic conditions were unfavorable for an anastomosis. In two of these cases, the esophageal segments could not be approximated, so a catheter was left in the esophagus in the hope that secondary healing might occur over the catheter. This plan was not successful because of the regurgitation of gastrostomy feedings into the extrapleural wound. Had the multiple-stage operation been undertaken in these infants, they might have been saved, but until Doctor Ladd demonstrated the completed antethoracic esophageal tube today, I must confess that I had been distinctly unenthusiastic about the use of the multiple-stage plan, even when a primary anastomosis was impossible.

In regard to Doctor Daniel's remark concerning the anesthesia, the first several cases in this series were operated upon under local anesthesia. It was in these cases that the considerable mobility of the two segments and the resulting tension upon the anastomosis was first observed. I feel that the operation of primary anastomosis is more difficult when undertaken under local anesthesia, and I believe it can be done more quickly, with less trauma to the two segments during the construction of the anastomosis and with a better anastomosis if it is done under general anesthesia.

# THE DANGER AND PREVENTION OF CITRATE INTOXICATION IN MASSIVE TRANSFUSIONS OF WHOLE BLOOD\*

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THE VALUE OF BLOOD TRANSFUSIONS in improving and widening the scope of surgery has become more and more appreciated. By the use of adequate blood before and during operations, emphasis is placed on the prevention of, rather than the treatment of shock. Likewise, the maintenance of the normal volume and constituents of circulating blood is an important factor in the prevention of anoxia. Since anoxia may occur in the absence of cyanosis, especially in the anemic patient, prevention rather than active treatment is much more desirable<sup>1</sup>. A third purpose served by blood transfusions is the improvement or maintenance of blood plasma proteins, a factor of importance in the healing of wounds and a satisfactory postoperative convalescence<sup>2, 3, 4</sup>.

The amount of blood loss during major surgery has frequently been grossly underestimated. This loss was not fully appreciated until recently when actual determinations were made. With the improvement of diagnostic methods and an appreciation of the physiologic needs of the patient, extensive surgical procedures have become more frequently used. In spite of attention being given to careful hemostasis, blood loss in many of these operations has been considerable. Actual determinations made following some thoracic operations have revealed that 1500 cc of blood is an average loss for lobectomy and pneumonectomy<sup>5</sup>. In some instances the loss was as much as 3000 cc. Extensive abdominal and thoraco-abdominal as well as other operations not infrequently cause a loss of 1500 to 3000 cc, or more, of blood.

Since the above factors have become appreciated, an attempt has been made in this hospital to replace the blood, while it is being lost, with an equal amount of whole blood or plasma, chiefly the former, in order to maintain the circulating blood in a normal state. This has necessitated the giving of massive transfusions, frequently from 1500 to 3000 cc and at times as much as 7000 cc. Blood studies following operations in these patients revealed values which compared favorably with those found before operation. There were no untoward reactions observed in these patients.

Recently, investigative work on the use of massive transfusions of blood and blood substitutes has been reported and a warning issued against the too liberal use of citrated blood. In an attempt to find a suitable blood substitute

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for replacement of blood loss from massive hemorrhage, Ivy, and his co-workers,<sup>6</sup> conducted extensive experiments on dogs. The animals were bled from 45 to 65 per cent of their estimated blood volume within a period of 3 to 20 minutes. If no replacement of this loss was made, approximately 84 per cent of the dogs died, when the loss was rapidly replaced by citrated whole blood or plasma over a five-minute period, 50 and 70 per cent of the dogs, respectively, died. However, if replacement was made with heparinized plasma only six per cent of the dogs expired.

From the results of these experiments the authors warned against the rapid replacement of blood loss with massive transfusions of citrated blood. They postulated that if 1500 cc–2500 cc of citrated whole blood or plasma were given rather rapidly to a 70-Kg man after a severe hemorrhage, it might prove to be fatally toxic.

Bruneau and Graham<sup>7</sup> reported experiments in which dogs were bled 10 per cent of the estimated blood volume and the blood then reinjected during a one-half hour period. The reinjected blood contained either 0.6 per cent sodium citrate or heparin. The hemorrhages were repeated until the animals died. The dogs receiving the citrated blood expired after an average of 9.25 hemorrhages, or approximately 92.5 per cent of the estimated blood volume, while the dogs receiving heparinized blood averaged 25.2 hemorrhages, or 252 per cent before death occurred.

The authors believed that some other factor than sodium citrate contributed to the deleterious effects in this group. However, they warned against the too liberal use of citrate in large transfusions.

In view of these two reports it was thought worth while to review the data on massive whole blood and/or plasma transfusions given during the past 18 months to 53 patients on several Surgical Services at the University of Chicago Clinics. A complete report<sup>8</sup> of this study was presented at the February meeting of the Society of University Surgeons held at Nashville, Tennessee, and will appear in "Surgery."

This series of 53 patients includes 35 abdominal, 16 thoracic, and two extremity operations. The volume of blood and/or plasma administered was 1500 to 3000 cc in 40 patients, and 3000 to 7000 cc in the remainder. The rate of administration was 1500 to 2500 cc given over a period of two to six hours in most patients. Sodium citrate, 2.5 Gm for each 500 cc of whole blood, and 4.0 Gm for each 500 cc of plasma was the anticoagulant routinely employed.

The blood pressure on some of the above patients fell below 80 mm Hg during operation, but shock was seldom seen following the transfusion. According to blood studies made before and following operation no patient was overtransfused and their good postoperative condition emphasized the importance of replacement of blood loss. Transfusion reactions such as pulmonary edema or acute hemolysis from mismatched blood were not observed.

It is obvious from the data presented that the clinical experience with



massive transfusions of citrated blood in our patients was at variance with the views that Ivy, and his coworkers, gained from their investigation. Thus, experiments were planned to test the influence of various factors which might contribute to the harmful effects of massive transfusions of citrated whole blood.

#### EXPERIMENTAL METHODS

Mongrel dogs weighing 7 to 14 Kg were given morphine sulphate Gm 0.015 and novocaine infiltration or ether anesthesia. Ether was found to be very satisfactory and was employed in most of the animals while the vessels were being cannulated, after which the administration of anesthesia was discontinued. All animals which survived the experiment were observed for two days or longer for evidence of citrate intoxication. Nonsterile technic was used in cannulating the femoral vessels for kymographic recording of arterial blood pressure, bleeding and the administration of blood or solutions. Kymographic tracings of respiratory activity were made by means of a bellows secured to the chest and connected with a mercury manometer.

DOG 654    Wt 11.3 Kg    Novocaine  
Sodium citrate 0.24 gm/Kg    (0.4% sol) in 10 minutes

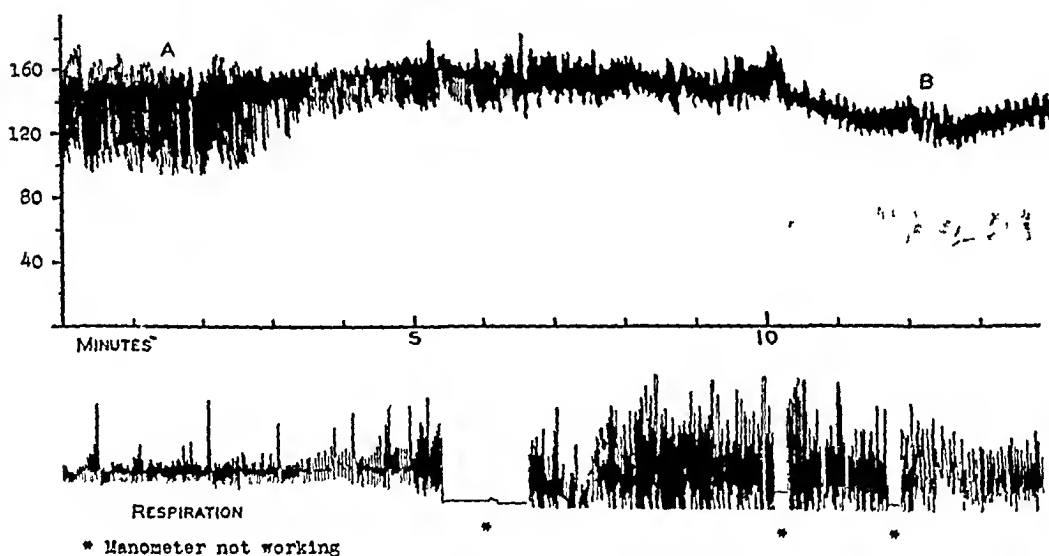


FIG 1—Dog 654. Injection of sodium citrate was begun at A and ended ten minutes later at B. Note relatively little alteration of blood pressure curve. There was some increase in respiratory activity during the latter half of the period of injection. The animal showed no late citrate reaction.

#### TYPES OF EXPERIMENTS

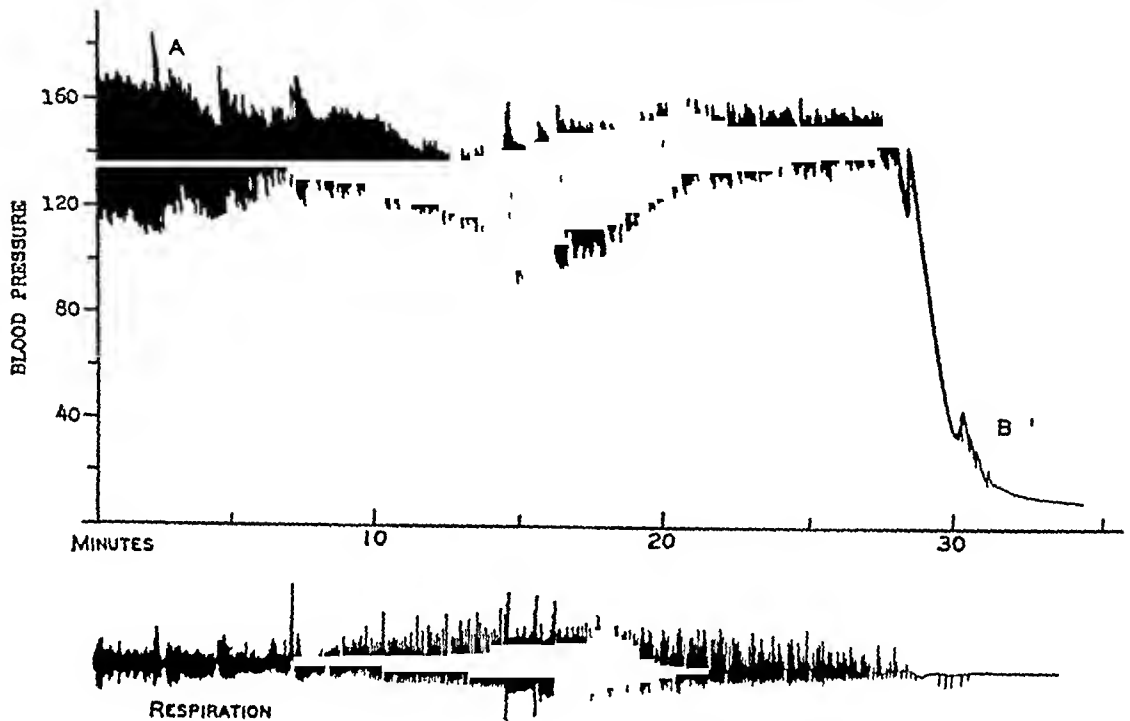
1 *The Effect of Sodium Citrate in Normal Dogs*—This was studied in 23 animals which were divided into three groups according to the amount of sodium citrate per kilogram of body weight injected. As seen in Table 1, they were subdivided according to the rate of administration of the solution. In Group A the animals received 0.18 to 0.25 Gm/Kg of body weight. The rate of administration varied from 2.5 to 30 minutes as may be observed

# CITRATE INTOXICATION

in the table Two of five animals receiving this dosage in 25 to 10 minutes died One of the four animals receiving the injection in 11 to 20 minutes expired, whereas all of four animals receiving the administration in the 30-minute period survived Figure 1 shows kymographic tracings of arterial blood pressure and respiratory activity of Dog 654 which survived 0.24 Gm

FIG 2

DOG 671 Wt 11.8 Kg Ether  
Sodium Citrate 0.40 gm /Kg (2.5% sol ) in 30 minutes



DOG 665 Wt 10.5 Kg. Ether  
Sodium citrate 0.95 gm /Kg. (2.5% sol ) in 2 hours

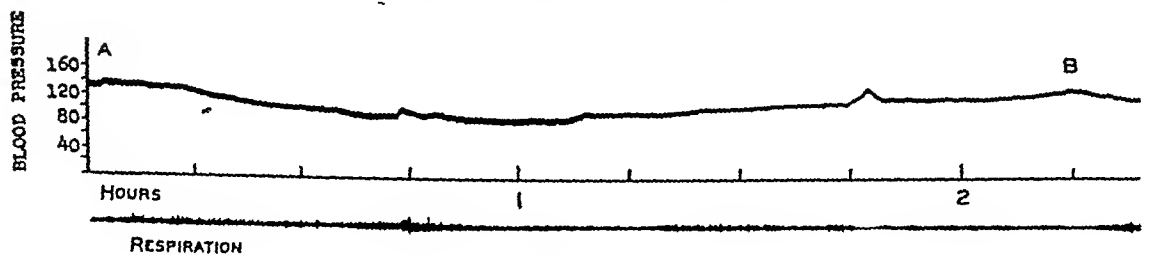


FIG 3

FIG 2—Dog 671 The injection of citrate was begun at A and was stopped at B Note relatively little alteration in blood pressure tracing until the sudden drop shortly before the injection was completed Some increase in respiratory activity is seen during the middle portion of the injection No attempt was made to revive the animal

FIG 3—Dog 665 Injection of sodium citrate was begun at A and continued until B Note relatively little alteration in blood pressure or respiratory activity throughout the injection The dog was followed for 25 weeks and showed no evidence of citrate reaction

of sodium citrate per kilo of body weight (or sufficient to cover 60 per cent of the estimated blood volume) given intravenously during a ten-minute period

In the second group of four animals, 0.29 to 0.40 Gm/Kg of body weight of sodium citrate were given in 13 to 30 minutes—and all of the

animals died. Figure 2 shows the tracings of Dog 671 which died following the intravenous administration of 0.40 Gm/Kg body weight of sodium citrate (2.5 per cent solution) given over a 30-minute period.

In the third group, six animals received 0.47 to 1.03 Gm/Kg of sodium citrate. Two of the six received the injection in 18 to 33 minutes—and both animals expired. In the remaining four, the administration time was 90 to 120 minutes. Three of this latter group survived. (See Fig. 3)

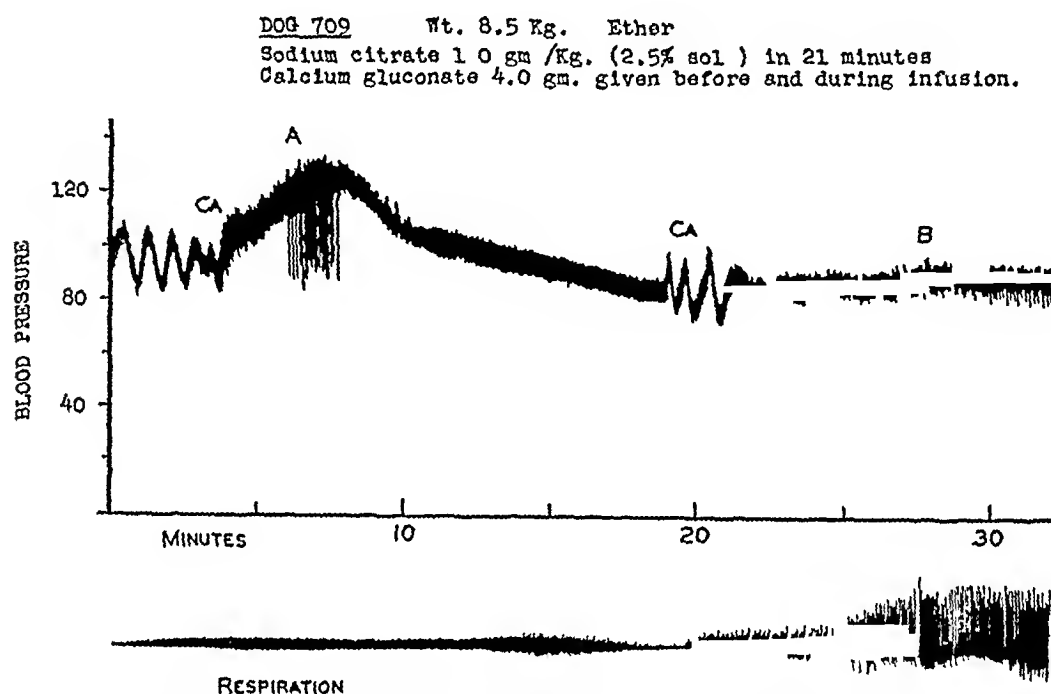


Fig. 4—Dog 709. Two grams of calcium gluconate were given at the first Ca and the injection of sodium citrate was begun at A. A second injection of calcium gluconate (2 Gm) was given at the end of 20 minutes and the injection of sodium citrate completed at B. The blood pressure was approximately the same at the end of the experiment as at the beginning and little change was noted in respiratory activity. The animal showed no evidence of citrate intoxication following the experiment.

From the above experiments it was concluded that normal dogs tolerate approximately 0.25 grams of sodium citrate per kilogram of body weight (or sufficient to cover 60 per cent of the estimated blood volume with a 0.41 per cent solution) when not injected too rapidly (over a period of 20 minutes or longer).

2 *The Influence of Calcium Gluconate on Citrate Intoxication in Normal Dogs*—In four animals, 0.87 to 1.14 grams of sodium citrate per kilogram of body weight were injected during a period of 20 to 38 minutes. When signs of citrate intoxication occurred, calcium gluconate, four to six grams (20 per cent solution) were slowly administered in divided doses. One of the animals expired due to a delay in the injection of the calcium. Figure 4 shows the tracing of Dog 709 which survived following the intravenous injection of 1 Gm of sodium citrate per kilogram of body weight, given over a 21-minute period. Calcium gluconate 4 Gm were given before and during the infusion (total of 4 Gm).

These experiments demonstrate that when ionizable calcium is made available, a higher concentration and a larger amount of sodium citrate may be given more rapidly without fatality (1 Gm per kilogram in 20 to 28 minutes)

3 *The Effect of Autotransfusion with Citrated Whole Blood Following a Hemorrhage of 20 to 60 per cent of the Estimated Blood Volume*—Eleven

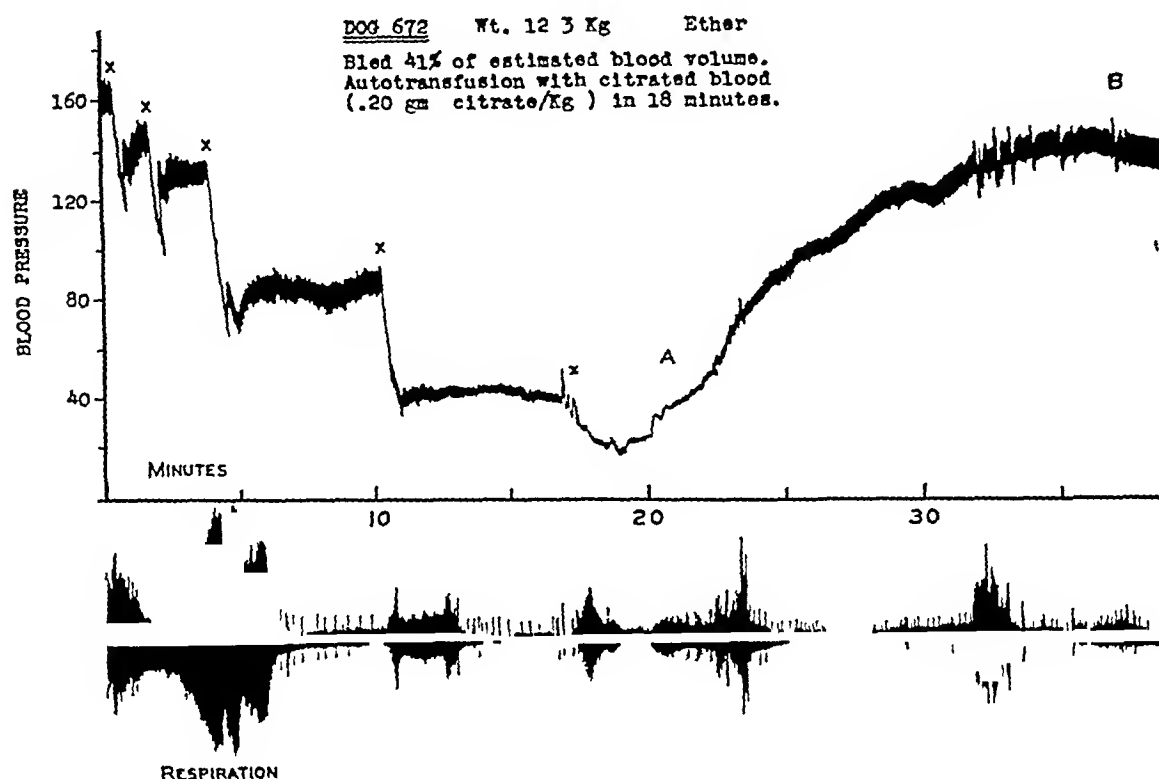


FIG 5—Dog 672 The dog was bled 100 cc at the five points marked X for a total of 500 cc. Replacement of citrated whole blood was begun at A and ended at B. Note return of blood pressure to approximately the prehemorrhage level. The animal was followed for one week and showed no evidence of late citrate reactions.

dogs were bled into a receptacle containing sodium citrate until they were in extreme shock (blood pressure from 30 to 45 mm Hg). The citrated (0.41 per cent) blood was then used for transfusing the animal. In three animals 0.14 to 0.21 Gm of sodium citrate per kilogram of body weight was introduced with the transfusion during an 11- to 12-minute period. All three animals expired. In the remaining eight dogs, 0.12 to 0.25 Gm/Kg of sodium citrate were administered in the transfusion over a period of 18 to 36 minutes. All of these animals survived.

Figure 5 shows the tracing of Dog 672 in which severe shock was produced by bleeding 41 per cent of the estimated blood volume. The blood was citrated (0.41 per cent) and returned to the animal in 18 minutes, with survival of the animal.

These experiments demonstrate that normal dogs will tolerate replacement with citrated whole blood after severe shock due to hemorrhage of 20 to 60 per cent of the estimated blood volume (using sodium citrate to cover

35 to 60 per cent of the blood volume) when given over a period of 20 to 35 minutes

4 *The Influence of Calcium Gluconate in Autotransfusion with Citrated Whole Blood Following a Hemorrhage of 26-70 per cent of the Estimated Blood Volume*—As in the preceding group, these animals were bled into a known amount of sodium citrate. When an extreme degree of shock was reached the citrated blood was then given intravenously. Four animals received 0.24 to 1.0 Gm/Kg of sodium citrate in the transfusion given over a period of 3 to 13 minutes without fatality. Four to 7 Gm of calcium gluconate

DOG 697 Wt 8.0 Kg Ether

Bled on three occasions, 76%, 76.7% and 83% of estimated blood volume. Autotransfusion with citrated whole blood in 7, 5 and 3 minutes. With the 1st & 3rd transfusions, calcium gluconate (4 gms) was given when signs of citrate intoxication appeared.

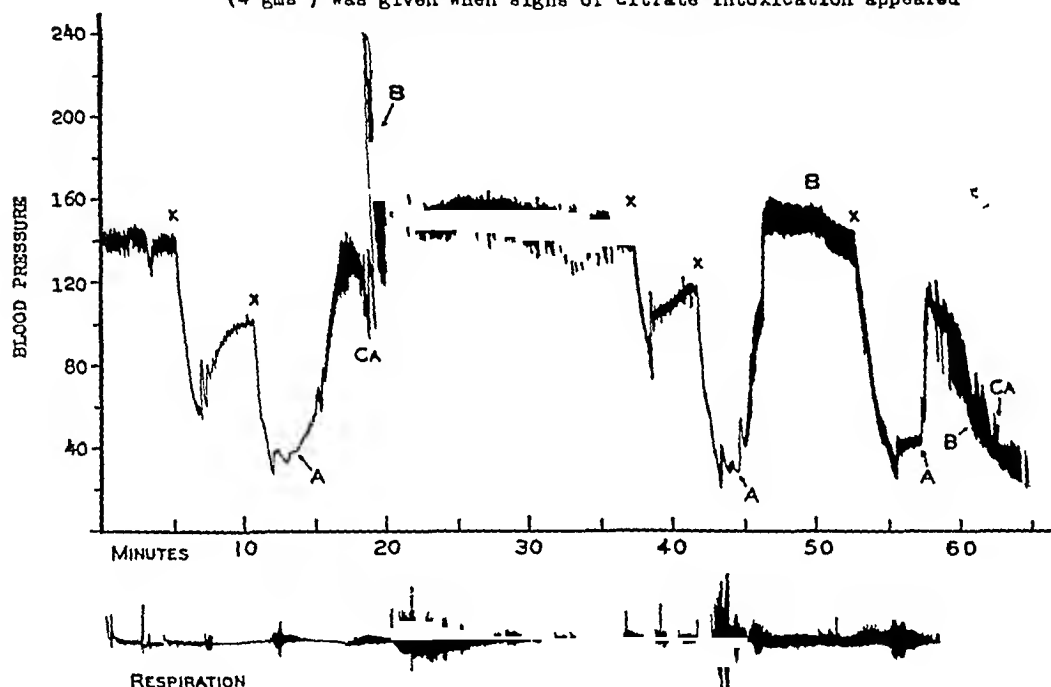


FIG 6—Dog 697. The first bleeding of 610 cc is indicated by the first two Xs. Replacement with citrated whole blood was begun at A and ended at B. At CA when citrate intoxication was becoming manifest 4 Gm of calcium gluconate were rapidly injected and produced an immediate rise in blood pressure. A second hemorrhage of 614 cc produced at the 2 Xs was made approximately 17 minutes after the first replacement was completed. Replacement with citrated whole blood was begun at A and ended at B with no evidence of citrate reaction. A third hemorrhage of 665 cc was made at X and again replacement was started at A and ended at B. Following this last replacement note marked citrate intoxication from which the animal could not be revived by the use of 4 Gm of calcium gluconate.

were used (See Fig 6—Dog 697). Thus, it is seen that a larger blood loss and replacement with a higher concentration of sodium citrate given more rapidly (3 to 13 minutes) was tolerated when calcium gluconate was administered.

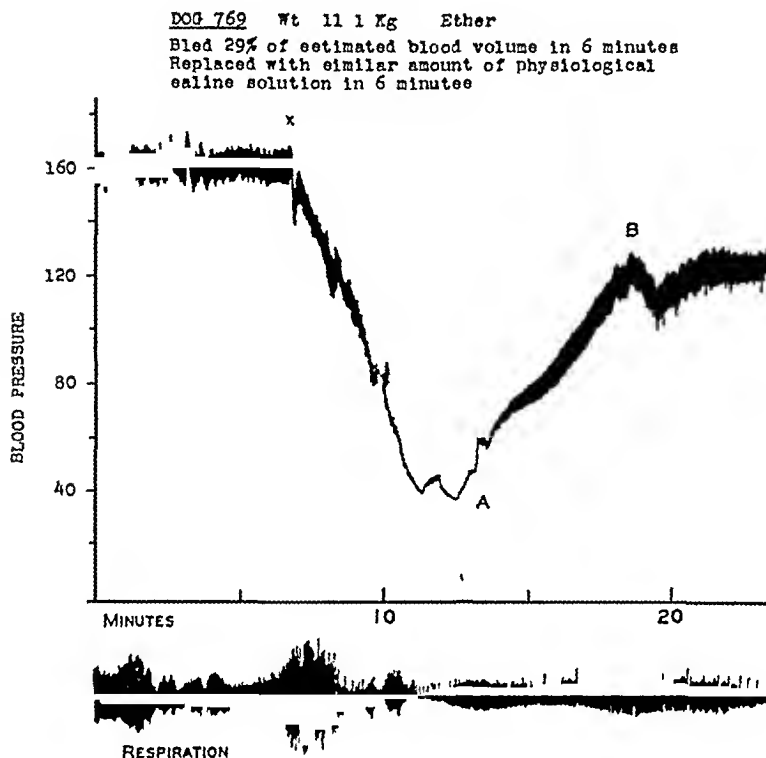
5 *The Replacement of Blood Loss with Physiologic Saline Solution Following a Hemorrhage of 27 to 50 per cent of the Estimated Blood Volume*. Eleven dogs were bled until extreme shock was produced. In five of these, replacement of the blood loss with an equal amount of physiologic

saline in a period of four to six minutes was carried out with no deaths. In the remaining six animals, replacement of the blood loss was made with an equal amount of physiologic saline plus the use of 3.3 to 6.0 Gm of calcium gluconate over a period of 3 to 18 minutes. All of these animals survived (See Fig 7). Thus, bleeding of 30 to 50 per cent of the estimated blood volume and replacement with a similar amount of physiologic saline, with or without the addition of calcium gluconate, administered in 3 to 25 minutes was well tolerated.

6. *Simultaneous Bleeding and Replacement of Blood Loss with Prepared Citrated (0.41 per cent) Whole Blood With and Without the Administration of Calcium Gluconate*—A *Without Calcium Gluconate* The amount bled in four dogs varied from 80 to 132 per cent of the estimated blood volume. The rate of bleeding varied from 37 to 165 minutes. Sodium citrate, 0.5 to 0.73 Gm/Kg of body weight were received in the transfusion. Two of the four animals survived. One of these was bled and transfused approximately 90 per cent of the estimated blood volume over a period of two hours. The other was bled and transfused 80 per cent of the estimated blood volume over a period of one hour. A third animal was bled and transfused 87.4 per cent of the estimated blood volume over a period of 30 minutes, at which time he expired. The fourth was bled and transfused 132.3 per cent of the estimated blood volume over a period of 2.75 hours. At the end of that period the bleeding and transfusion were stopped when a rapid blood pressure fall was observed. The blood pressure then returned spontaneously to normal. However, the animal expired approximately one hour later (See Fig 8).

B *With Calcium Gluconate* (4.0 to 8.0 Gm) —Eight animals are included in this group and were either given small amounts of calcium gluconate during the period of transfusion, or the injections of calcium gluconate were given when the blood pressure fall indicated that the dog would no longer survive. The eight animals were bled and transfused approximately 100 to 200 per cent of the estimated blood volume over a period of from one to two hours. The amount of sodium citrate received in the transfused blood was from 0.5 to 1.0 Gm/Kg of body weight. When calcium gluconate was withheld until citrate intoxication was manifest, the blood pressure fell rapidly and the arterial blood became very dark. Respiratory activity sometimes remained unchanged, but was usually somewhat more active. Three of the eight dogs were allowed to bleed 150, 100 and 180 per cent of their estimated blood volume until the blood pressure fell to 60, 42 and 30 mm Hg, respectively, before calcium gluconate was injected. All three responded immediately to calcium gluconate and survived the experiment (See Dogs 933, 997 and 2 of Table II). All eight of the animals survived following the injection of calcium gluconate. Figure 9, Dog 997, shows the blood pressure and respiratory tracing during bleeding and replacement of 175 per cent of the estimated blood volume in two hours. Four grams of calcium gluconate were used.

Fig 7



DOG 818 Wt 8.5 Kg Ether  
Bled 132% of estimated blood volume in 3 hours with simultaneous  
transfusion of citrated blood (0.83 gm/Kg of sodium citrate)

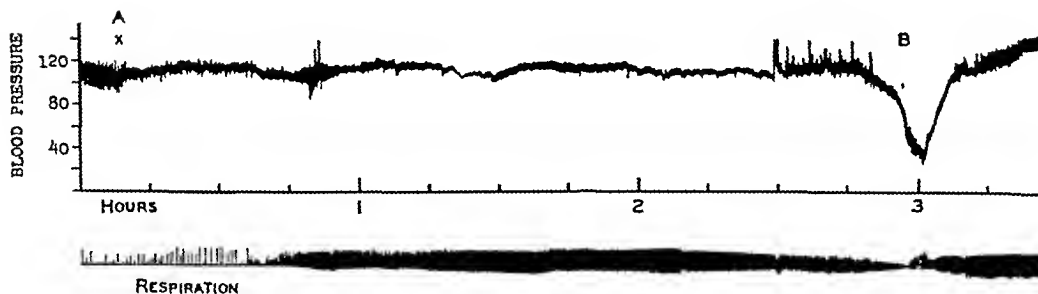


Fig 8

FIG 7—Dog 769 Bleeding was begun at X and continued for approximately six minutes when a total of 325 cc had been removed. Replacement with physiologic saline solution was begun at A and ended at B. Note return of blood pressure to a somewhat lower level than was present before the hemorrhage. The animal died two days following the experiment of distemper.

FIG 8—Dog 818 Bleeding and transfusion of citrated (0.41%) whole blood were begun at A and continued until B when both bleeding and transfusion were stopped. Note continued lowering of blood pressure to approximately 25 Mm of mercury and spontaneous return to the same level as before experiment was begun. Tetanic contractions were observed after the blood pressure returned to a normal level. The dog expired approximately one hour following the completion of the experiment.

From these experiments it was concluded that normal dogs tolerate simultaneous bleeding and transfusion of citrated whole blood amounting to as much as 75 to 125 per cent of the estimated blood volume. When calcium gluconate was added, as much as 200 per cent of the estimated blood volume was removed and replaced without fatality.

COMMENT—Since the introduction of transfusion of citrated blood in 1915 by Lewisohn,<sup>9</sup> considerable study has been made regarding its value and its disadvantages. Many of the reactions attributed to the citrate during its early use<sup>10, 11</sup> have subsequently been proven to be on the basis of pyrogenic substances or to mismatching of the blood<sup>12, 13</sup>.

The toxicity of sodium citrate was demonstrated in dogs by Lewisohn,<sup>9</sup> and in man by Krautwald and Dorow.<sup>14</sup> These workers found that large doses of citrate were necessary to produce harmful effects and that the rate of injection was an important factor (Krautwald and Dorow). This was likewise the case in our experiment. When the rate of injection of sodium citrate alone or as citrated blood was comparable to transfusions of 1000 cc of blood per hour in man, as much as 0.24 Gm/Kg of body weight, or sufficient for use in 60 per cent of the estimated blood volume, was safely tolerated. If the administration was over a very short period, i.e., sufficient citrate for 60 per cent of the estimated blood volume given in 10 to 12 minutes, the action was usually fatal. This latter finding was similar to the results of Ivy, and his coworkers, who found that a high percentage of animals expired following replacement of severe blood loss by citrated whole blood or plasma during a five-minute period. It would be practically impossible however to duplicate clinically so rapid a rate of administration, since this would necessitate the giving of over 4000 cc of blood to a 70-Kg man during a five-minute period.

In the group of 11 animals in which physiologic saline solution was used to replace loss of blood from severe hemorrhage, no untoward effects were noted. These animals were followed for some time following the experiment and no late reactions were manifested. The amount of hemorrhage was sufficient to produce extreme shock in all cases. Our results did not compare with those of Ivy, and his coworkers, in this regard, although the rate of administration was practically the same, namely, four to six minutes. It appeared to make little difference when calcium gluconate was given with the saline solution.

In the group of 12 animals where replacement of blood loss with citrated whole blood was carried out simultaneously with the bleeding, the procedure was similar to that described by Bruneau and Graham. Some degree of fall in blood pressure was produced in their animals with each successive bleeding, and perhaps might have accounted for the shorter period of time which their animals survived (approximately 9.25 bleedings or 92.5 per cent of the estimated blood volume in 4.5 hours) as compared with ours (approximately 11.2 per cent of the estimated blood volume in 11 hours). The results of their experiments agree with ours in that animals may tolerate



the replacement of massive blood loss with citrated whole blood when given at the rate currently employed in man, namely 500 to 1000 cc of blood per hour. Our experiments would seem to indicate that animals in whom shock has been produced are able to tolerate citrated whole blood somewhat less well than animals in whom shock is prevented by the administration of

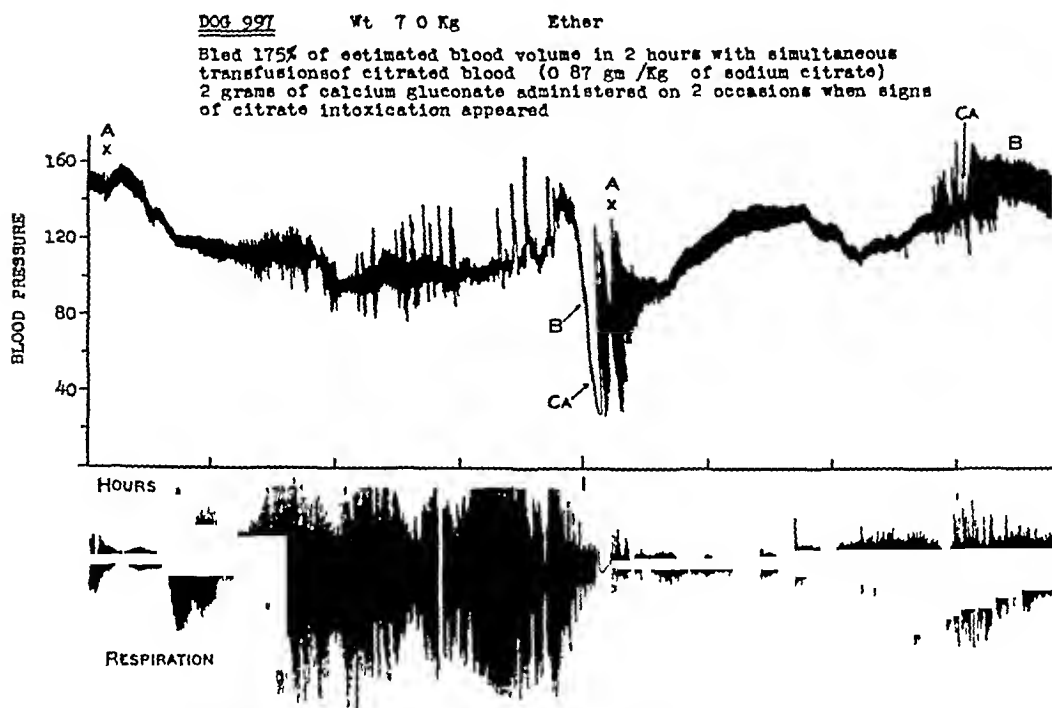


FIG 9—Dog 997 Simultaneous bleeding and transfusion of citrated (0.51%) whole blood were begun at A. Note change in character of blood pressure tracing beginning one half hour after the experiment started, with a sudden fall occurring approximately one hour after the experiment was begun. Both bleeding and transfusion were stopped at B at which time a sample of arterial blood was removed for study. The arterial blood was extremely dark and the eye reflexes were almost absent. Two grams of calcium gluconate were injected at Ca (near the bottom of the blood pressure tracing) with almost immediate response of cardiac and respiratory activity. The color of the blood and the eye reflexes returned to normal within two or three minutes. Bleeding and transfusion were again started at Ax. Towards the end of the second hour, 2 Gm of calcium gluconate were again injected along with the transfused blood. This raised the blood pressure to approximately the preexperimental level. Bleeding and transfusion were discontinued at B. The animal was followed for a period of three weeks and showed no evidence of late citrate reaction.

citrated whole blood during the bleeding period. Thus, it would seem that the rate of administration of citrated blood should be somewhat slower in those patients where severe shock has already been produced by massive hemorrhages.

The picture of citrate intoxication was similar regardless of the type of experiment in which it was observed. Alterations in blood pressure tracings were at times observed for several minutes prior to a rapid terminal fall. (See Figs 8 and 9) Likewise, some change in respiratory activity was usually present for several minutes before fatal intoxication occurred. Respiratory failure was never observed prior to cardiac failure. Muscular reactions were variable although some of the experiments were made under local anesthesia. Definite tetanic contractions were present in some of the

latter group when citrate intoxication occurred. Eye reflexes usually became very sluggish and were at times completely absent when extreme intoxication occurred.

The blood findings in severe citrate intoxication were quite dramatic. The color of the blood became very dark red (almost black) and gas analyses revealed that the oxygen was as low as three to four volumes per cent. Severe acidosis was observed, the  $p_H$  falling from an original 7.4 down to as low as 7.15. This was thought to have been due in part at least to the use of citrated blood which showed a marked reduction in serum carbon dioxide and had a  $p_H$  of 7.25. The mechanism of citrate intoxication is under further investigation at the present time.

*The Use of Calcium Gluconate in Preventing or Treating Citrate Intoxication* Calcium gluconate was used to prevent citrate intoxication both where sodium citrate alone was given to normal animals, and when it was used in blood for the replacement of blood loss. In either case it was extremely effective in preventing or overcoming citrate intoxication. Within a period of two to three minutes, the blood pressure and respiratory activity returned to normal. The color of the blood which had become extremely dark also returned to a normal bright red and gas analyses revealed a normal oxygen content. The eye reflexes which had become very sluggish returned to a normal state. The amount of calcium usually employed in 7 to 14 Kg animals was approximately 4 Gm (20 cc of a 20 per cent solution) for the replacement of 60 to 100 per cent of the estimated blood volume. When animals were allowed to bleed as much as 200 per cent of the estimated blood volume, as much as 8 Gm were given. The experiments were not carried further than 200 per cent of the blood volume, and all of the eight animals which received calcium gluconate in this group survived the experiment.

The clinical application of calcium therapy in citrate intoxication has already been reported by Hill and Muirhead<sup>15</sup>. In the use of concentrated plasma the danger of citrate reactions is somewhat greater than in the use of citrated blood due to the increased amount of citrate needed. These authors stated that citrate reactions in their clinical experience were a rarity. They, however, produced this condition intentionally in four patients, the reaction being prevented or stopped once it had developed, by the use of 3 to 10 cc of calcium chloride or calcium gluconate. In view of our experiments it would seem desirable to have calcium gluconate or calcium chloride available for immediate use when massive transfusions of citrated blood were expected to be administered over an extremely short period of time.

#### SUMMARY AND CONCLUSIONS

Massive transfusions of citrated whole blood for the treatment of extreme shock (blood pressure of 30–45 mm Hg) produced by hemorrhage of as much as 60 per cent of the estimated blood volume were safely tolerated in dogs when the replacement of blood loss was made during a period of 20 minutes or longer.

TABLE I  
EFFECT OF SODIUM CITRATE IN NORMAL DOGS

Amount of Sodium Citrate—in Gm /Kg of Body Weight	Time of Infusion	Number of Dogs	Died
A 0 18-0 25	2 5— 10 minutes	5	2
	11 — 20 minutes	4	1*
	30 —	4	0
B 0 29-0 40	13 — 30 minutes	4	4
C 0 47-1 03	18 — 33 minutes	2	2
	90 —120 minutes	4	1

\* Received 0 25 Gm /Kg in a 15 minute period

Showing the effect of sodium citrate in 23 normal dogs Note that the rate of injection was an important factor in the production of intoxication

TABLE II  
SIMULTANEOUS BLEEDING AND REPLACEMENT WITH CITRATED (0 41%) WHOLE BLOOD

Dog No	Per Cent of Estimated Blood Volume Bled	Time in Hours	Calcium Gluconate	Results
793	90	2	None	No ill effects observed Sacrificed 48 hours
811	80	1	None	No ill effects observed Sacrificed 8 days
816	87 4	0 66	None	Died Sudden fall in blood pressure Blood very dark
818	132 3	2 75	None	Died Sudden fall in blood pressure Blood very dark
896	101	1	6 Gm	No ill effects Sacrificed 8 days
898	105	1	4 Gm	No ill effects Sacrificed 12 days
899	122	1 25	4 Gm	No ill effects Sacrificed 4 days
916	200	2	8 Gm	No ill effects Died 3 days PO—wound infection
933	150	1 5	4 Gm	Revived with calcium after bleeding 150% of estimated blood volume Sacrificed 18 days
937	200	2	8 Gm	Revived with calcium after bleeding 75% Sacrificed 4 days
997	175	1 75	4 Gm	Revived with calcium after bleeding 180% Died 5 days of infection
2	200	2	6 Gm	Revived with calcium after 100% bleeding Sacrificed 3 weeks

Detailed results in 12 animals which were bled and transfused with citrated (0 41 per cent) whole blood simultaneously Eight of the animals received calcium gluconate when signs of toxicity were present or during the experiment preventing intoxication by the citrate All of the animals receiving calcium gluconate survived the experiment

When bleeding and transfusions were conducted simultaneously, an average of 112 per cent of the estimated blood volume was exchanged during a period of 70 minutes before the animal expired This would correspond to a transfusion of 7840 cc of blood given during the same period of time for a 70-Kg man When the rate of bleeding and transfusion was less rapid, a larger volume was exchanged without reaction

Thus, a large margin of safety is present even in massive transfusions of citrated whole blood or plasma when the administration is at a maximum rate currently employed in man (1000 cc per hour)

Calcium gluconate was very effective in preventing or alleviating citrate intoxication when very large doses of citrate had been administered during a short period of time

We are indebted to Dr Lillian Eichelberger for the blood studies made in this experiment

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# SURGICAL MANIFESTATIONS OF COCCIDIOIDOMYCOSIS\*

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AN INTERESTING DEVELOPMENT associated with the war's world-wide migration is exposure to circumscribed endemic disease. This focuses attention on hitherto local problems such as coccidioidomycosis, sometimes known as California disease, Valley fever, or coccidioidal granuloma.

The disease occurs in two forms, localized and disseminated. The latter form, or coccidioidal granuloma, was first reported in the United States by Rixford<sup>1</sup> in 1894. Only one previous case, that reported by Psodes and Wernicke<sup>2</sup> in 1892, from the Argentine, occurs in the world literature.

On account of its unusual features and grave prognosis, the disease attracted great attention. In 1938, Dickson and Gifford<sup>3</sup> discovered that an influenza-like state affecting residents of the San Joaquin Valley was in reality the primary, or localized, form of coccidioidomycosis. This disease has been referred to also as San Joaquin fever, Valley fever, and desert rheumatism. Smith,<sup>4</sup> in 1940, and Emmons,<sup>5</sup> in 1943, have made important contributions to its epidemiology.

In addition to the San Joaquin Valley, the disease is endemic in certain arid regions of Arizona, New Mexico, Mexico, and Texas. In the latter state the distribution of cases is fairly widespread (Fig. 1). There are also endemic foci in the Chaco region of Argentina and in Italy, two cases having been reported by Jocano<sup>6</sup> from the general area of the present battlefields.

The causative organism was first thought to be protozoan, but, in 1900, Ophuls and Moffet<sup>7</sup> proved it to be a fungus. There are two phases in its life cycle, a vegetative and a parasitic. In tissue the organisms appear as double contoured spherules of variable size containing endospores. The appearance of these spherules is characteristic and their identification in tissue is diagnostic of the disease (Fig. 2). The endospore-containing spherules grow out on artificial culture medium, suitable soil or vegetation as a white fluffy mold. Microscopically, the growth is composed of interlacing mycelia with tiny chlamydospores attached to the aerial hyphae.

Infection in the primary form is the result of inhalation, or, rarely, inoculation of the chlamydospores which have grown out on the soil or vegetation of the endemic areas. A recent epidemic<sup>8</sup> has been traced to inhalation of dust, and the chlamydospores were recovered from the soil which was the source of the dust. Several recent mild epidemics<sup>9, 10</sup> have occurred in soldiers encamped in an endemic area. Emmons<sup>5</sup> attaches considerable importance to certain wild rodents in the area of infection and states that the

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## COCCIDIOIDOMYCOSIS

disease is primarily a rodent disease which is transmitted frequently, but accidentally, to man through the medium of contaminated soil.

It is unlikely the disease can become established in new areas by the migration of infected persons. Other factors such as climate and perhaps the presence of suitable animal species as hosts are necessary. Man to man contact transmission is unknown. The parasitic spherule is not very infectious and must first grow as the vegetative form. All authorities agree it is pointless to isolate patients with the disease. However, care should be taken in the disposal of sputa and dressings.



FIG 1—Showing the fairly widespread distribution of coccidioidomycosis in Texas

The primary disease in an endemic area is widely distributed. In the San Joaquin Valley three-fourths of the ten year residents have been infected. Outside of the endemic areas traces of the disease can be found. In an Eastern Preparatory School of 680 students, 17, or 2.5 per cent, showed evidence of past primary infection (Aronson and Gallagher<sup>11</sup>). None of these had previously been diagnosed.

The secondary form or coccidioidal granuloma is much rarer. It occurs about once for every three to four hundred primary cases. Approximately 790 cases of coccidioidal granuloma have been recorded to date. It is not due to reinfection but to a failure of the host to localize, or keep localized, his primary infection. Development of the granulomatous form usually quickly occurs following the primary infection, but in certain cases the interval may be years. This fact plus a migrating population indicates the probable occurrence of cases of the granulomatous form in many new areas. The problem is, therefore, of general as well as local interest.

The primary infection is commonly accompanied by signs and symptoms

of a mild respiratory infection, usually bronchitis, with a productive cough. In addition, there may be chills, fever, anorexia, malaise, backache, and joint pains. Within the first 18 days erythema nodosum appears in 2 per cent to 15 per cent of cases.

The leukocyte count is variable. Eosinophilia occurs fairly regularly late in the disease. The sedimentation rate is usually elevated. The sputum contains the diagnostic spherules during the active stage. If they are not found in wet preparations, the sputa may be cultured. If the fungus is present, it can be identified by animal inoculation and recovery of the spherules.

Roentgenograms may reveal only transient changes in the lung fields. Sometimes there are nodular areas of pneumonitis. Exudative lesions may be associated with cavitation. The cavities are usually single, may close spontaneously, but have a tendency to persist. Cavitation is the only lesion of surgical interest occurring in the primary phase.

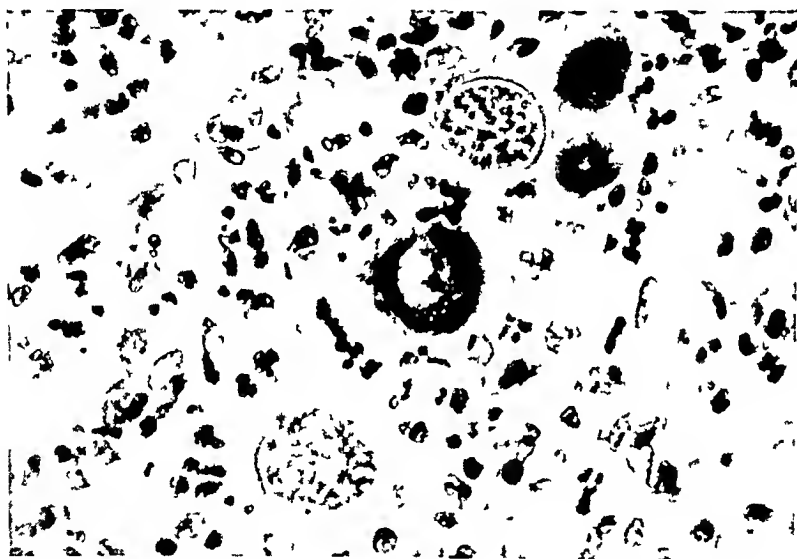


Fig. 2—*Coccidioides immitis*. Photomicrogram of the organism in tissue.

Once the primary infection has been localized a high degree of immunity develops. Patients once having had the disease react to an extract of the organism somewhat as to tuberculin. This coccidioidin test depends on a skin sensitivity to a polysaccharide substance combined with a nitrogenous radical and is an allergic manifestation. The usual dilutions used are 1:1000 and 1:100. The test is read at 24, 48, and 72 hours. Recovered cases<sup>4</sup> have reacted as long as nine years after the primary infection. The test is relatively disease-specific. A negative<sup>9</sup> reaction tends to exclude the possibility of infection, while a positive indicates past or present infection. There is also a complement fixation test and a precipitin reaction. It is said that in disseminated granuloma complement fixation titer is high and precipitin titer is low.

When the infection is overwhelming, or the host's resistance inadequate, dissemination occurs. The disseminated form is more common in young adult

males Any tissue of the body can be involved except the gastro-intestinal tract The individual lesions are usually granulomatous cold abscesses A variety of surgical conditions can be simulated The following cases are illustrative

#### ILLUSTRATIVE CASE REPORTS

**Case 1**—A 31-year-old soldier was admitted to the Station Hospital, Randolph Field, Texas, August 4, 1943, complaining of pain in the RLQ of his abdomen of two weeks duration The pain was intermittent For the two days prior to admission it had grown progressively worse and was associated with nausea, vomiting and anorexia The past history was entirely negative He had never been outside of Texas Physical examination revealed no abnormal findings except well localized tenderness in the RLQ of the abdomen, marked rigidity of the right rectus muscle, and rebound tenderness The white blood count was 11,000 with 76 per cent polys A diagnosis of appendicitis



FIG 3—Case 1 Roentgenograms showing partial atelectasis of the right lower lobe and involvement of the 7th and 8th dorsal vertebrae, with rib invasion

was made and the abdomen opened The peritoneum was thickened and minute tubercles were noted on the bowel The mesenteric nodes were enlarged Postoperatively, the patient developed a persistent atelectasis in the right chest He was transferred to Brooke General Hospital Roentgenograms of the chest showed, in addition to the partial atelectasis of the right lower lobe, a destructive lesion in the transverse processes of the seventh and the eighth dorsal vertebrae The temperature was elevated daily to 102° F The atelectasis in the right lung field cleared The abdominal wound healed *per primam* The pathologist reported the presence of *Coccidioides immitis* in the tubercles on the mesentery of the removed appendix The lesion in the thoracic spine spread rapidly and there was invasion of the ribs (Fig 3) Coccidioidin skin test, dilution 1:1000, was negative The patient's condition was rapidly downhill and he expired on September 23, 1943 The duration of the disease was approximately two months Necropsy revealed widespread infiltration of the lungs, peritoneum, vertebrae meninges, liver, spleen, and kidneys Microscopic study of the lesions showed the presence of large numbers of *Coccidioides immitis*

**Case 2**—A 20-year-old soldier entered Brooke General Hospital October 12, 1943, complaining of pain in the upper abdomen This had started about three months prior to admission It was not affected by the taking of food Anorexia and weight loss were marked There were daily elevations of temperature The past history was negative



He was a native of North Carolina and had been stationed at Fort Clark, Texas, for six months. At Fort Clark Station Hospital an abscess in the right groin had been incised under local anesthesia. Roentgenologic examination showed evidence of a mass to the left of the dorsal vertebrae (Fig 4). A transfer diagnosis of "Pott's disease" was made. On admission to Brooke General Hospital, physical examination revealed a draining sinus in the right groin. There was an abscess, about 5 cm in diameter, to the right of the lumbosacral junction. The patient was acutely ill. Temperature ranged to 104° F. Bacteriologic studies of the material from the lesions in the right groin and back were negative. Gradually another abscess developed over the vertex of the skull, and roentgenograms showed destruction of both tables of bone. It was then decided to excise the infected cranial bone, and this was done, November 2, 1943. All infected bone was curetted out and the wound closed. The pathologist found the



FIG 4

FIG 4—Case 2. Roentgenogram showing evidence of mass to the left of the dorsal vertebrae.

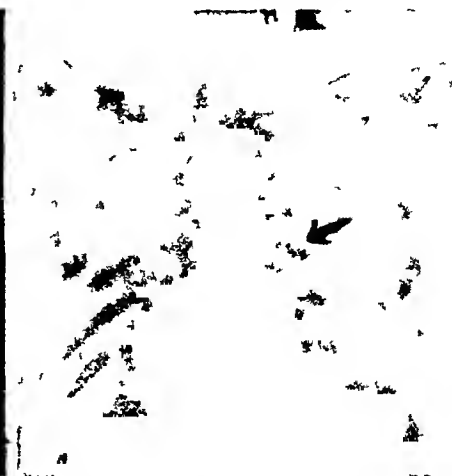


FIG 5

FIG 5—Case 3. Roentgenogram showing areas of consolidation in both lung fields, with widening of the mediastinum.

typical diagnostic spherules in the material removed at operation. The scalp wound did well for a short period but thereafter the wound broke down, with evidence of secondary infection. The patient's course was rapidly downhill, with widespread dissemination of the lesions, and he expired November 24, 1943. Duration of disease was approximately four months. At autopsy, there was widespread involvement of the lungs, bones, liver, spleen, kidneys and pancreas. Microscopic study of the infected tissues showed the presence of *Coccidioides immitis* in great number.

**Case 3**—A 22-year-old soldier entered the Station Hospital, Moore Field, Texas, August 7, 1942, complaining of cough and generalized weakness. Past history was negative. He was a native of Oregon, and had been stationed at Moore Field for one year. The clinical diagnosis was pneumonia. Roentgenograms of the chest showed areas of consolidation in both lung fields, with widening of the mediastinum (Fig 5). There was a rather large node behind the right sternomastoid. Laboratory studies revealed a white count which varied from 10,000 to 24,500, with a rising eosinophil count of 2 per cent to 33 per cent. He was transferred to Brooke General Hospital and September 12, 1942, the lymph node was removed from the neck. A diagnosis of coccidioidomycosis was made by microscopic study of the node and identification of *Coccidioides immitis*. Coccidioidin skin test, dilution 1:1000, was negative. The patient's course was rapidly downhill, with widespread dissemination of the infectious process. He expired October 22, 1942. Duration of disease was approximately eight weeks. Necropsy was done, and the pathologic diagnosis of coccidioidomycosis, with involvement of the lungs, lymph nodes, liver, spleen, adrenals, kidneys, skin, meninges, and brain established.

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**Case 4**—A 30-year-old soldier entered the Station Hospital, Hondo Field, Texas, September 3, 1943, complaining of pain in the lower portion of his back, coughing and occasional gastric upsets. He had been a resident of Tennessee, and had been stationed at Hondo Field for six months. Physical examination was entirely negative except for the presence of a daily febrile reaction to  $102^{\circ}$  F. Complete laboratory and roentgenologic studies were done—all of which were negative, with the exception of a secondary anemia. Later, there was a progressive rise in eosinophils up to 30 per cent. He was transferred to Brooke General Hospital, October 21, 1943, undiagnosed. Examination showed a tender mass, about 5 cm. in diameter in the region of the left sacro-iliac spine.



FIG 6—Case 4. A Showing punctate mottling of each lung field. B and C Showing bony involvement, with marked destruction of the vertebrae and ribs.

It was fluctuant, but on aspiration very little pus could be obtained. Roentgenograms of the spine were normal. In the chest there was a punctate mottling of each lung field (Fig 6A). A second fluctuant mass developed over the sternum. Aspirated material from this, now revealed *Coccidioides immitis*. Coccidioidin skin test, dilution 1:100 and 1:1000 was negative. The patient's course was rapidly downhill with daily temperature elevation of  $103^{\circ}$  F. A granulomatous skin lesion developed on the left side of the nose. Bony involvement, with marked destruction of the vertebrae and ribs was demonstrated late in the disease (Fig 6B and 6C). The patient expired January 27, 1944. Duration of the disease was approximately four months. Autopsy was

performed and the diagnosis of coccidioidomycosis, with involvement of lungs, bone, peritoneum, meninges, skin and subcutaneous tissue, lymph nodes, kidneys, and adrenals was established

Our cases illustrate the clinical similarity of coccidioidal granuloma and certain common surgical conditions. It is probable that more of these cases will find their way to the surgical wards in various parts of the country. The diagnosis of coccidioidal granuloma is often surprisingly easy. The chief difficulty is overlooking the possibility of its occurrence on account of its rarity. This can be avoided by suspecting it in all cases suggesting tuberculosis in which the tubercle bacillus is not found. The coccidioidin test was of no value in our cases. This is probably due to the overwhelming infection. The demonstration of the organism in tissue or pus is the final stage in the diagnosis. It may be surprisingly easy.

Our experience in encountering these cases in the surgical wards is not unusual. This is attested by the fact that isolated instances of similar cases are depicted in the literature.

Martin<sup>12</sup> reports two cases studied of which one simulated a spinal cord tumor and the other a cerebellar tumor. Craig and Dockerty<sup>13</sup> found coccidioides in the wall of a cerebellar abscess. Foley, Low, Broders, and Helman<sup>11</sup> had a patient with coccidioidal osteomyelitis of the skull. Peers, Holman and Smith<sup>15</sup> and Winn<sup>16</sup> have discussed the surgical aspects of the pulmonary cavities. Ruddock and Hope<sup>17</sup> have reported a case of diffuse peritonitis. The joint changes are discussed by Rosenberg, Dockerty, and Meyerding.<sup>18</sup> McMaster and Gilfillan<sup>19</sup> report 24 cases having bone and joint involvement. Pipkin and Lehman<sup>20</sup> have diagnosed six cases of coccidioidomycosis with dermatologic lesions. In a personal communication to the authors, they reported excellent results with tartar emetic and roentgenotherapy.

The prognosis of the disease is grave. It is influenced largely by the rate of progression of the disease. All of our cases were of the acute type. In cases progressing less rapidly the prognosis should be better. Numerous instances of arrest of the disease are recorded. In general, however, 50 per cent of the cases of coccidioidal granuloma will die.

In coccidioidal granuloma, surgical removal, if at all possible, is probably the procedure of choice. This will be feasible in those rare cases in which the chlamydospores were inoculated into the skin and a localized granuloma resulted. Caldwell<sup>21</sup> reports such a case in which a child's toe was amputated and a cure resulted.

Various drugs, such as colloidal copper, tartar emetic, and iodides, have been advocated. Results are equivocal. Likewise, sulfonamide drugs<sup>18</sup> are of no value. Penicillin<sup>22, 23</sup> does not inhibit the growth of the mold in culture, and we have found it ineffective in the treatment of the disease. Jacobson<sup>24</sup> has claimed good results from the intravenous administration of coccidioidin. Recently, immune transfusions have been used with beneficial results in some instances.<sup>10</sup>

The pulmonary cavities are best treated conservatively. If hemoptysis is severe pneumothorax has given good results. Peers, Holman and Smith<sup>15</sup> report a case in which lobectomy was performed because of fear of dissemination. However in this case there was a post-lobectomy empyema and coccidioides was found in the discharge. In spite of this there was no dissemination. Other cavities in the same series were treated conservatively and with excellent results.

Blades<sup>25</sup> recently performed a lobectomy at Walter Reed General Hospital upon a patient with coccidioidomycosis in which a single large cavity was present in the left upper lobe. Hemoptysis had been present in this patient for two years. Surgery was performed solely because of the hemoptysis, and an excellent result was obtained.

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DISCUSSION.—DR. HOWARD C. NATHAN, San Francisco: The paper of Colonel Burch is particularly timely, for the profession will surely encounter the chronic forms of this disease in all parts of the country.

The acute form is contracted most often in the San Joaquin Valley and the Southwestern States. The infection is acquired quickly by newcomers and in certain of our cities in the infected areas 75 per cent of the population show positive coccidioidin tests. The annual reports of the Kern County Department of Public Health provide surprising figures. Only about one in five hundred of those who have the acute Valley Fever develop the chronic form, and these are the dark-skinned—the Negroes, Mexicans and South European types. The acute cases usually recover without sequelae or complications. In the later phases of the acute type about three per cent develop erythema nodosum and occasional erythema multiforme. Of those who develop the chronic or granulomatous form the mortality is given at about 55–60 per cent, although it is our impression that it may well be higher. There is no specific therapy.

The organisms are recovered from the soil and the prevalence in areas is indicated by the incidence of the infection in the rodents. The kicking up of dust on air fields is ideal for dissemination of the fungus.

At the University of California and the San Francisco Hospitals of 31 proved cases only three were of the acute form. Undoubtedly, we are slower to recognize the acute form than the practitioners in the infected districts. On the other hand we have had 29 of the chronic or granulomatous form. Seventy per cent of these were in men, which conforms to the general experience and one-third of all have been in the third decade of life. Dark-skinned men between 20 and 30 years of age are typical sufferers. Coccidioidal meningitis, in the absence of disseminated lesions, is apt to be missed. Because of internal hydrocephalus we have mistaken it for a posterior fossa tumor and recognized it only at operation. Involvement of the nervous system and its envelopes have been noted by Evans, Rand, Ingham, Courville, Morris, Craig and Dockerty.

In the University of California Hospital the chronic form has constituted 0.02 per cent of the total admissions in the last ten years.

Of the 29 chronic cases in both our hospitals the involvements have been

Lungs	10
Skin and subcutaneous tissues	9
Bone and joint	8
Meninges	4
Generalized	7

This totals 37, but in several there was asymptomatic lung involvement in addition to bone or skin changes

Any case of chronic disease from the San Joaquin Valley is suspect, and the similarity to tuberculosis in biologic and laboratory reactions and in the clinical manifestations is close

The coccidioidin skin test is a reliable index of those who have, or have had the disease, and it is probable that the sensitivity persists through life. The complement fixation test is evidence of the existence of the chronic or granulomatous affection. These with cultures, guinea-pig inoculations, direct recovery of the fungus from lesions, a high sedimentation rate and a moderate leukocytosis with some eosinophilia and spinal fluid culture are the diagnostic aids. Laboratory workers are prone to become infected. Of our 31 cases—29 of which were chronic—the recorded mortality was 34 per cent. Seven have disappeared, 12 are still alive. Two cures resulted where simple lesions of an extremity were treated by amputation.

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# EFFECTS OF BOVINE ANTERIOR HYPOPHYSEAL EXTRACT ON URINARY BLADDER TRANSPLANTS IN YOUNG DOGS\*

INCLUDING SOME OBSERVATIONS ON ITS EFFECTS ON  
ENDOCHONDRAL OSSIFICATION

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AUTOTRANSPLANTATION of urinary bladder mucosa into the abdominal fasciae of dogs and rodents causes bone formation in the connective tissue surrounding the transplant,<sup>1</sup> furthermore, in growing mice and guinea-pigs, growth and aging of cartilage and bone can be intensified and accelerated by the administration of anterior hypophyseal extract.<sup>2</sup> Correspondingly in immature guinea-pigs and in young rabbits, repair of fractured bones can likewise be promoted by injection of anterior pituitary extract<sup>3, 4</sup> and similarly, in urodele larvae, administration of anterior hypophyseal hormone enhances the various phases of regeneration subsequent to amputation of the tails.<sup>5, 6</sup>

It seemed, therefore, of interest to investigate, whether in young dogs bone formation around transplanted bladder mucosa might be affected by the administration of anterior hypophyseal hormone. At the same time we intended to determine whether this hormone might influence skeletal growth and aging in young dogs, as it does in growing rodents.

## MATERIALS AND METHODS

In ten young female dogs, urinary bladder mucosa was autotransplanted into the abdominal fascia. For this purpose, two incisions, approximately five centimeters in length, were made on either side of the upper abdomen. The anterior sheath of the rectus muscle was exposed and freed from all fat tissue. The bleeding points were controlled and the wounds packed with sterile gauze moistened with saline solution. By a low midline incision, the urinary bladder was exposed. A portion of the bladder tissue including the mucosa was removed, the bladder and the suprapubic wound were closed in layers. The excised bladder tissue, about 2.5 cm square, was stretched, the mucosal layer gently removed and divided into two equal sections. Under aseptic precautions, these parts of the mucosa were sutured with interrupted silk sutures to the rectus fascia.

Five animals served as noninjected controls. The injected dogs were divided into two groups. In the one, the extract was given soon after the operation, in the second the treatment with the extract was delayed for two

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weeks Bovine anterior hypophyseal extract, freshly prepared according to the method of Loeb and Basset, was injected intraperitoneally The daily dose varied from 20 to 30 cc depending on the weight of the animal The animals were sacrificed at intervals of 10, 12, 14, 28 and 42 days

#### GROSS OBSERVATIONS

There was no consistent change in the weights of the injected animals One injected dog died of pneumonia At the autopsy of the remaining injected dogs, the cartilage of the knee joint revealed enlarged vessels and hypertrophy This condition was not observed in the noninjected animals Furthermore, whereas in the noninjected animals, the chondro-osseous junction of the ribs was even and smooth, in the injected dogs, it showed a bead-like swelling These changes were slight after two weeks of injections, but they became more accentuated, if the injections were continued for four or six weeks In the injected dogs, spleen, liver and kidney were found to be grossly unchanged, with the exception of one animal, whose spleen was twice the usual size The endocrine organs did not show any changes with the exception of the thyroid glands which were enlarged in all cases The grafts did not exhibit noticeable alterations

Tissue from the transplants, the chondro-osseous junction of the ribs, the thyroid glands, ovaries and pancreas, and in some instances liver and spleen were taken for histologic examination The bones were fixed in 10 per cent formalin, decalcified, embedded in celloidin and stained with hematoxylin-eosin The other tissues were embedded in paraffin and likewise stained with hematoxylin-eosin

#### HISTOLOGIC EXAMINATION

*Thyroids* In the noninjected dogs, the tissue was composed of small and medium-sized acini separated from each other by a thin layer of connective tissue The acini were filled with hard homogeneous colloid, and lined by flat or cuboidal epithelium with narrow cytoplasm and dense nuclei

After 10 or 14 days of injections, the cells lining the acini had increased in size and become more numerous The nuclei were larger and more lightly stained than ordinarily, and some of them showed mitotic division The acini were more closely packed together than normally In some areas, the colloid was softer than usual, and contained scattered phagocytes The supporting connective tissue stroma was loose in texture and contained larger amounts of fluid than in controls This condition had not greatly changed after four weeks of injections After six weeks of treatment, the acinar epithelium had become flatter and the colloid harder again, the thyroid had thus returned to a resting state

In the other organs, there was no marked change In the ovaries, atresia and luteinization of the follicles were very much accentuated

*Cartilage and Bone* In normal dogs, sections through the chondro-osseous junction of the ribs, revealed a sharp demarcation of the cartilaginous zone from the osseous part Most cartilage cells were resting and small The



central portions of the costal cartilage exhibited some small foci of liquefaction. These areas were here and there replaced by bone marrow. Towards the bony part of the ribs the cartilage cells were larger and showed a regular columnar arrangement and in a single cartilage row, seven to ten columnar cells were counted. The layers of hypertrophic cartilage were narrow and consisted of one to three cells. Underneath the hypertrophic cartilage a transverse bony lamella began to form. All these findings indicated that the dogs used in these experiments were nearing the end of their growth period. The capillary loops surrounding the hypertrophic cartilage cells were moderately filled with blood and only a few osteoblasts were found in close approximation to the cartilage. The bony spicules were thin and short. The bone marrow was cellular. The periosteal tissue was scarce, dense and fibrillar.

After 10, 12 or 14 days of injections the layer of the hypertrophic cartilage was enlarged. More cartilage cells than usual had become hypertrophic. In the distal part there was no intensified proliferation of the cartilage but in the center it had undergone increased disintegration. In the subchondral zone, the capillaries showed a pronounced congestion, connective tissue cells proliferated markedly by way of mitosis and formed epithelioid cells that were packed closely together and filled the intertrabecular spaces of the metaphysis. Many of the proliferating cells formed new bony substance and accordingly the spicules were more numerous and thicker than in the noninjected animals.

Farther distally, some of these proliferating connective tissue cells had coalesced and formed multinucleated osteoclastic giant cells. The periosteal connective tissue was likewise increased in amount. Both the periosteal production and resorption of bone were intensified. In the vascular canals the perforating vessels were congested.

After four or six weeks of injections, both the hypertrophic and regressive changes of the cartilage were still more accentuated, however, even at these later stages, a resumption of growth of the cartilage was not noted. In the subchondral zone, the amount of thickened trabecular bone was still greatly increased, but resorption of osseous substance became more prominent. Along the periosteal and to a lesser extent, the endosteal surface of the shaft, increased amounts of connective tissue containing numerous osteoclastic giant cells were observed. However, these changes remained restricted to the area adjoining the junction with the cartilage and did not involve the region around the bone marrow.

#### TRANSPLANTS OF BLADDER EPITHELIUM

The transplanted bladder epithelium grew out, forming thereby a cyst. Two weeks subsequent to grafting the cells of the transplant were enlarged, whereas the newly grown epithelium, lining the cyst, formed a single layer of rather flat or cuboidal cells. The adjacent connective tissue was increased in amount. In one of four cases small epithelioid cells had accumulated in

# ANTERIOR HYPOPHYSEAL EXTRACT

FIG 1

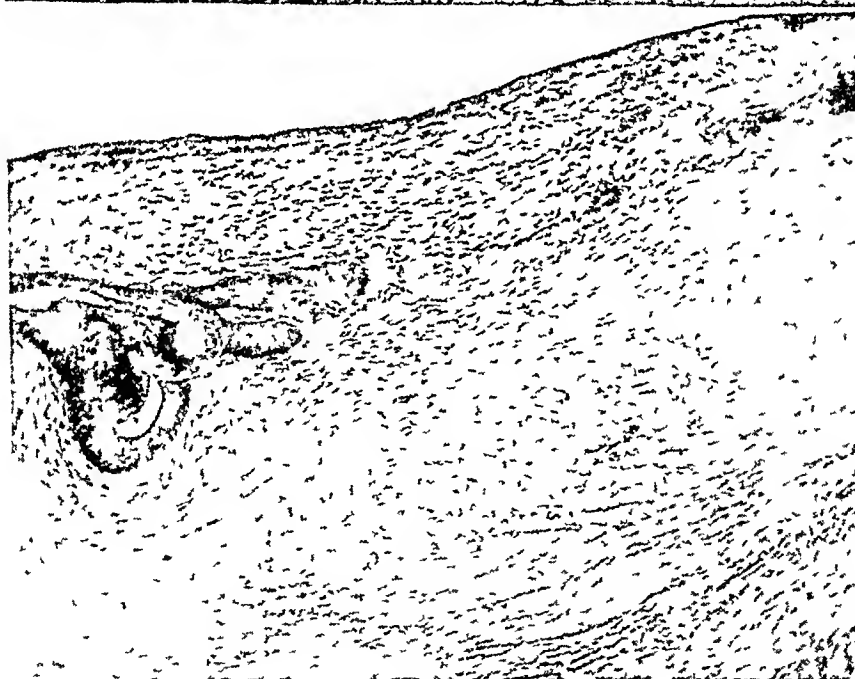


FIG 2

FIG 1—Section through autotransplanted urinary bladder epithelium after two weeks transplantation (control)  
No bone formation has taken place

FIG 2—Section through autotransplanted urinary bladder epithelium after two weeks transplantation. The animal had received 14 injections of 20 cc anterior hypophyseal extract daily subsequent to transplantation  
Bone formation around the transplant. The epithelium is partly hypertrophic

FIG 3



FIG 4

FIG 3—Section through autotransplanted urinary bladder epithelium after six weeks transplantation (control)

Bone formation around the transplant

FIG 4—Section through autotransplanted urinary bladder epithelium four weeks following transplantation. The animal had received 28 injections of 20 cc anterior hypophyseal extract daily for four weeks following transplantation

Larger amounts of denser and more mature bone than in Figure 3. Epithelium hypertrophic

a collagenous and slightly calcified connective tissue, and had assumed a bead-like arrangement along the surface of the collagenous material. In the remaining three cases, collagenous connective tissue had been formed, but epithelioid cells were lacking.

Four or six weeks subsequent to transplantation, the bladder epithelium had undergone marked hypertrophy, but at the same time regressive changes leading to vacuolation were also pronounced. In all cases, the connective tissue adjoining the cyst had been converted into cancellous bone containing bone marrow and multinucleated osteoclastic giant cells.

In the dogs, injected with anterior hypophyseal extract for 10, 12 or 14 days, the bladder epithelium showed pronounced hypertrophy, as well as vacuolation and liquefaction. Thus, the degree of regressive changes seen at this time was comparable to that noted in noninjected animals four or six weeks following transplantation. The fibrillar connective tissue network was distended by fluid, the fibroblasts were markedly enlarged and more numerous than in the noninjected dogs at the corresponding stage. Farther away from the cyst, and in the periphery of the loosened connective tissue large amounts of dense collagenous connective tissue were found exhibiting deposits of calcium. Here, numerous osteoblasts and preosteocytes had deposited osseous substance. True bone was present in three of four cases injected for 10 to 14 days, whereas in the fourth case, the bone formation was only suggested, being as yet in an early stage. Thus, as compared with conditions in noninjected dogs, bone formation was accelerated and farther advanced subsequent to the administration of the hypophyseal hormone.

After four or six weeks of hormonal treatment, the regression of the epithelium had made more progress and had spread into further areas. The connective tissue which adjoined the bladder epithelium and was loosened at the earlier stages, had become dense, collagenous and more fibrillar. Calcification in close approximation to the cyst was greatly increased, in addition larger amounts of cartilage were present. Considerable amounts of mature cancellous bone had been formed and encroached upon the epithelium of the cyst, while resorption of bone by osteoclasts was accentuated. The condition, thus, was comparable to that seen in noninjected dogs after three and more months subsequent to transplantation.

COMMENT In young dogs, administration of bovine anterior hypophyseal hormone causes hyperplasia and hypertrophy of the thyroid gland, similar in kind, but less in degree than that observed by Loeb,<sup>7</sup> and his coworkers, in growing rodents.

In the costal cartilage, the cells showed some hypertrophy, regressive changes were intensified, but no stimulation of proliferative process in the cartilage occurred. Endochondral, as well as peritrabecular and periosteal bone formation was increased during the earlier stages. Subsequently, however, the increased ossification was followed by intensified vascular and cellular resorption.

Under the influence of anterior hypophyseal extract, the transplanted

bladder epithelium underwent swelling associated with or followed by, accelerated and intensified regressive processes. The connective tissue adjoining the transplant took up large amounts of fluid. The collagenous connective tissue, subsequently formed, was denser and contained more calcium salts than in the noninjected animals. In the injected animals, the development of both cartilage and bone was markedly accelerated and intensified. Bony spicules were present as early as 12 or 14 days following transplantation, whereas, in noninjected dogs as a rule only a piceous substance was present in the neighborhood of the cyst during the first 14 or 16 days after transplantation, and bony tissue was observed 19 days after transplantation (Copher and Key,<sup>5</sup> and Huggins<sup>9</sup>) at the earliest.

The unusually early appearance of piceous substance 14 days after transplantation in one of our noninjected dogs might be attributed to the fact that this animal was younger than the others. As reported previously the hormonal effect on bone and cartilage is more marked in younger than in older animals.

In the injected dogs, the maximum of ossification was reached after four weeks of treatment with the hormone, whereas in the noninjected dogs the peak of bone formation was observable two months following transplantation. However, the amount of bone formed and the state of maturity of the osseous substance were similar in injected and noninjected animals at later stages of the experiments. This is probably due to the fact that in the animals receiving the anterior hypophyseal hormone not only the formation but also the resorption of bone were intensified.

A satisfactory explanation of the formation of bone in the fascial connective tissue adjoining the transplants of urinary and also of gallbladder epithelium has as yet not been given. Apparently, this heterotopic ossification occurs only, if a variety of conditions are met in the transplant as well as in the host tissue. Active growth and subsequent regression of the transplanted epithelium seem to be prerequisites. Development of larger amounts of dense connective tissue, precipitation of calcium salts and insufficient nutrition of tissues are known to favor bone formation.<sup>10</sup> The peculiar ability of the epithelium of the urinary tract to become the site of heterotopic ossification is also exemplified by the appearance of bone in the renal pelvis after ligation of the vascular pedicle. It is conceivable that a state of malnutrition in the transplanted tissue might lead to a disturbed metabolism of the growing mucosa which would be conducive to regression and to ossification of the surrounding tissue. Possibly, the high phosphatase content of the urinary tract epithelium may also be a factor in the heterotopic bone formation. But, the rôle of this enzyme can only be of secondary significance since transplanted epithelium of the small intestine which is also rich in phosphatase does not lead to ossification in the connective tissue. Whatever the mechanism underlying bone formation may be, its course is accelerated and intensified under the influence of anterior hypophyseal extract. We, thus, have to deal with another instance in which

anterior hypophyseal hormone accelerates the course of a developmental process

Previous observations have demonstrated the acceleration of regeneration of amputated limbs in salamanders and frogs<sup>7, 8</sup> and of bone repair in growing guinea-pigs and rabbits treated with anterior hypophyseal extract<sup>3, 4</sup>

The rate with which these processes take place in the noninjected animals, may be represented by a curve, which has been termed the time-curve by Leo Loeb and all processes of growth, development and aging of various organs and tissues have their peculiar time-curve, which is genetically determined<sup>11</sup> The latter, however, according to Loeb, can be accelerated and intensified, or delayed, and weakened by various hormones The acceleration of bone formation seen after administration of anterior hypophyseal hormone in the connective tissue adjoining the urinary bladder transplants may thus be considered as an acceleration of the time-curve of this process as compared with its course in noninjected animals

#### SUMMARY

Administration of anterior hypophyseal extract accelerates the formation of cancellous bone occurring in the abdominal fascia around urinary bladder transplants of young dogs This effect represents another instance of an acceleration of a tissue time curve by anterior hypophyseal hormone The cartilage at the chondro-osseous junction of the ribs undergoes increased hypertrophy and regression under the influence of anterior hypophyseal hormone, but its proliferation could not be stimulated in the young adult animals The production, as well as the resorption, of bone could be temporarily increased by the hormone The skeletal effects of anterior hypophyseal hormone in the dog are, therefore, similar to those exerted by this hormone in mice and guinea-pigs

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## EXPERIMENTAL STUDY OF THE HISTOPATHOLOGY OF BURNS WITH PARTICULAR REFERENCE TO SITES OF FLUID LOSS IN BURNS OF DIFFERENT DEPTHS\*

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IT IS AXIOMATIC that the key to understanding certain lesions of many organs is a knowledge of the special features of their blood supply. Yet, singularly little attention has been paid to the special features of the blood supply of human skin in discussions of the pathology of burns or in their classification. With the present-day emphasis on local fluid loss as a cause of burn shock, however, it becomes important to review the pathology of burns in relation to the blood supply of skin because it is from blood vessels that fluid is lost. Such a study is herewith reported.

### MATERIAL AND METHODS

*Selection of a Suitable Experimental Animal*—In preliminary experiments made on several common laboratory animals we tried to produce burns that resembled fairly superficial human burns. We were unable, however, to produce burns on the backs of these animals that demonstrated the erythema and blister formation that characterize this type of burn in man. This led us to reflect that the skin of man serves a different purpose from the skin of most very hairy and furry animals and, for this purpose, it has a very different blood supply. The skin of man serves as an organ for disseminating heat when the weather is hot and, hence, it is equipped with sweat glands and an extensive set of small blood vessels situated close to the epidermis. As our work progressed it became apparent that these superficial plexuses of vessels are responsible for the erythema and blister formation of superficial burns and that many common laboratory animals lack this extensive superficial blood supply because their skins are designed to serve primarily as insulation rather than as organs for disseminating heat. Hence,

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Appreciation is due A. W. Carrie and E. C. Hunt who gave valuable assistance in performing the experiments.



these manifestations of superficial burns (erythema and blisters) cannot be produced in them. The histopathology of superficial burns in many laboratory animals, then, differs profoundly from that in man. We found, however, that the skin of the hog is similar to the skin of man in many respects. Wilson<sup>1</sup> points out that it is one of the few animals whose skin contains papillae. It sweats in hot weather and so, like man, uses its skin to disseminate heat. Its skin, therefore, contains a reasonably extensive plexus of small vessels in the papillary and subpapillary layers of the dermis and an abundant supply of sweat glands (Fig 1). The hog, then, was selected as the experimental animal for these studies.

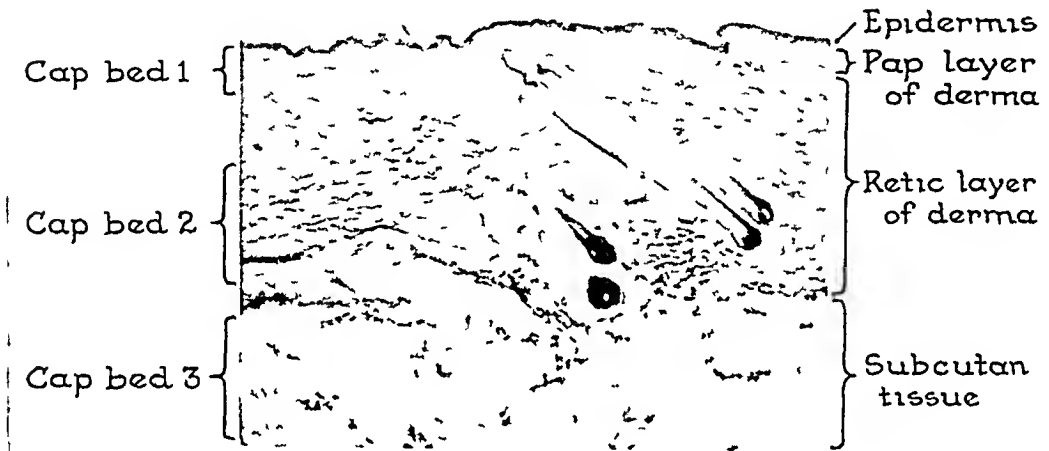


FIG 1—Low power photomicrograph of the skin of the back of a young hog. The location of the superficial plexuses normally concerned in the process of heat loss, and primarily concerned in superficial burns, is indicated as Cap bed 1. The roots of the hair follicles and the secreting portions of the sweat glands are situated in pockets of areolar tissue in the lower portion of the derma. Three such pockets can be seen in this photograph. Cap bed 2, which is primarily concerned in the more severe second degree burns, is confined to these pockets.

*Methods for Producing Burns*—Young hogs, recently weaned, and weighing around 15 kilos were used. They were anesthetized with ibatol, which was given either subcutaneously far removed from the burn site or intravenously. Burns were produced in two ways. By holding the base of a 25 cc Erlenmeyer flask of boiling water against the shaved skin of a hog for different lengths of time, or by dipping a portion of the shaved back of a hog into a large bath of water heated to 80° C for different lengths of time.

#### GROSS OBSERVATIONS

*"Red" and "White" Burns*—There is a great deal of variation in the response of the skin in different areas in the hog. The skin of the back is thick. A flask held against it for four seconds and then removed produces a burn which quickly turns red. If held for seven seconds the red is of a deeper color. When the flask is held for from 10 to 20 seconds the color tends to be patchy, with both red and white areas present over the burned

surface. The white areas, moreover, tend to turn gradually red. But when the flask is held for from 25 to 30 seconds most of the burned skin is white and it tends to remain white. The skin of the abdomen requires much shorter exposures to produce the same effects.

In first degree burns produced by very short exposures large blisters do not form. But in the more severe superficial burns the epidermis tends to be raised slightly by underlying fluid and when it is lifted off its under surface can be seen to be wet.

In the more severe first degree burns and in second and third degree burns produced by this method the swelling is more noticeable. The swelling is greatest in the burns produced with the longer exposures and where the skin is thinnest.

In the larger burns produced by dipping the back of the hog into a water bath the gross appearances were similar to those observed after holding a flask against the skin. The time necessary to produce comparable burns, however, was different.

*A Method for Determining the Depth of a Burn in the Hog*—It was observed that information could be gained about the depth of a burn in the hog by pulling on the hairs remaining in the burned areas. If the burn is superficial the hairs offer as much resistance to being pulled out as do hairs in normal skin but if the burn is deep the hairs offer little resistance to being pulled out. The reason for this will be given later.

#### MICROSCOPIC OBSERVATIONS

Most of the substance of the skin of man and of most animals is relatively nonvascular. It consists chiefly of dense irregularly arranged connective tissue and the chief component of this is the intercellular substance collagen, a nonliving material. Hence, most of the skin does not need, nor is it supplied with, extensive networks of capillaries. There are, however, two important groups of capillary networks in the skin of man and the hog, (1) Several layers of networks situated in the papillary, and in the adjacent part of the reticular layers of the dermis together with loops extending up into papillae, these are concerned with allowing the skin to lose heat and they also nourish the epidermis above them, and (2) networks about the secreting portions of the sweat glands and the roots of hair follicles and also in the papillae of the latter. The sites of these capillary beds are indicated in Figure 1.

*First Degree Burns*\*—In very mild first degree burns, produced by exposures of two or three seconds, the only change that can be observed in

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\*The three-degree classification is used in this paper. A first degree burn is considered to be one in which damage is confined mostly to the epidermis, a second degree burn one in which damage extends into the dermis without, however, destroying all of it or the more deeply situated portions of the hair follicles and sweat glands, and a third degree burn one in which the whole-thickness of the skin, including the more deeply situated epithelial elements, is destroyed.

histologic sections is a dilatation and congestion of the capillary loops of the papillae (Fig 2, A) In slightly more severe first degree burns soon after the injury the capillaries of the papillae are dilated and congested and the lowermost cells of the epidermis above the papillae are hydropic Later accumulations of fluid lift the epidermis from the dermis as the hydropic cells give way (Fig 2, B) A little later the epidermis becomes separated from the dermis by a still larger accumulation of fluid (Fig 2, C) In fairly severe first degree burns there is also a marked congestion and dilatation of the blood vessels in the deeper part of the papillary layer and of the adjacent part of the reticular layer (Fig 3)

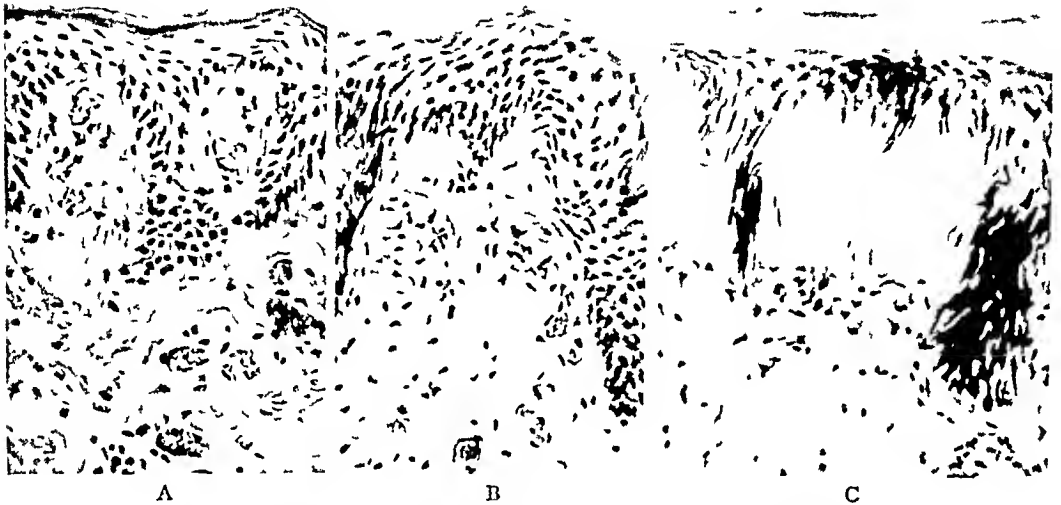


FIG 2—Medium power photomicrographs of hog skin showing the development of a blister in a superficial burn A Specimen recovered 15 minutes after a five second exposure to a flask of boiling water It shows dilatation and congestion of the capillary loops of the papillae and the small blood vessels of the papillary layer B Specimen recovered one hour after a five second exposure to a flask of boiling water It shows the same dilatation and congestion of vessels as is seen in A but, in addition, it shows an accumulation of fluid in and under the deepest cells of the epidermis which is breaking away from the dermis This illustrates the beginning of a blister due to plasma leaking from the adjacent congested capillaries C Specimen recovered four hours after a six second exposure to a flask of boiling water In this the epidermis has become almost completely separated from the dermis by fluid and is attached only at the sites of some of the interpapillary pegs

To sum up A histologic study of first degree burns shows that there is a dilatation and congestion of the superficial plexuses of capillaries and venules in the skin (the plexuses used for disseminating heat) and, in the more severe ones, that this is associated with an escape of fluid from these vessels Part of this fluid may lift the epidermis from the dermis to form small blisters, and part causes an edema of the dermis In our studies of burns in the hog we found that almost all blisters were situated between the epidermis and the dermis, and these findings make one question whether intra-epidermal blisters are as common in man as is generally believed, except in the skin of the palms of the hands and soles of the feet where the epidermis is thick

*Second Degree Burns*—In mild second degree burns many of the vessels in the superficial group of plexuses continue to function and leak fluid

In severe second degree burns the whole superficial group of vessels is

mostly sealed off by the heat ("white" burns) For a while we were greatly puzzled as to how there could be so much fluid loss in this type of burn because the underlying dermis, as such, contains few capillaries It was not until our histologic studies revealed an intense congestion and dilatation of the capillary beds associated with the deep secreting portions of the sweat glands and the deepest parts of the hair follicles (Fig 4) that we found the answer This congestion is associated with fluid loss, and the fluid that escapes from the capillaries associated with the deepest parts of the hair follicles loosens the attachment of the hairs This explains why hairs can be pulled out so easily in this degree of burn—easily-pulled hairs signify



FIG 3—Low power photomicrograph of a fairly severe superficial burn 48 hours after it had been produced It shows, particularly, the dilatation and congestion of the blood vessels other than capillaries (which cannot be seen at this magnification) situated in the outer portion of the derma The congested vessels appear black in the photograph

fluid loss in the capillaries associated with the bottoms of the hair follicles, and, hence, a deep second-degree burn In the hog, fluid lost from this capillary bed finds its way readily to the subcutaneous tissue

*Third Degree Burns*—In moderate second degree burns we did not observe evidences of great capillary congestion in the subcutaneous tissue and our findings suggest that much of the fluid that tends to accumulate in the subcutaneous tissue in this type of burn *has its origin in the skin*—it leaks down from the capillaries associated with the bottoms of hair follicles and secreting portions of sweat glands But in very severe second degree burns and in



FIG. 4—A Medium power photomicrograph of a deep portion of a hair follicle four hours after a flask of boiling water had been held against the skin for 30 seconds. Close inspection shows that the capillaries associated with the hair follicle are tremendously congested, so much so that it suggests that a hemorrhage had occurred in this tissue.  
B High power photomicrograph of the deep secreting portions of sweat glands from skin similarly treated. The capillaries about the sweat glands can be seen to be dilated and congested and the tissue containing them is distended with escaping fluid.

third degree burns fluid loss actually occurs from the capillaries of the subcutaneous tissue, we observed a marked congestion of the capillary beds in it and there were evidences of accumulations of fluid about them

#### EXPERIMENTS WITH TRYPAN BLUE

The histologic studies reported above indicated that two groups of capillary beds in the skin could be involved in burns of different intensities, and that a third capillary bed, situated in the subcutaneous tissue, is involved in more severe burns. It was thought that it would be helpful to perform another type of experiment to help confirm, or deny, that these beds are the chief sites of fluid loss in burns of different intensities.

Trypan blue is a colloidal dye which can be injected intravenously into animals in a 1 per cent solution without noticeable harmful effects. It does not ordinarily escape from healthy capillaries fast enough to produce a very intense diffuse staining of the animal's tissues. Where plasma is escaping into tissue, however, the trypan blue seems to escape as well, and so such areas become of a deep blue color. We injected several young hogs with up to 110 cc of 1 per cent solution per hog, either soon before or soon after burns were produced on them by the flask method. Thin slices of skin and subcutaneous tissue were removed from the burned areas at different time-periods, ranging up to three hours after the burns were produced, and examined with naked eye.

In general, the surface of first degree burns in an animal previously given trypan blue soon turns blue and slices taken from such burns, soon after the burn is produced, show a deep blue line along the superficial border of the dermis. Slices taken an hour or more later show the whole-thickness of the skin to be blue, but the most intense blue color is still at the upper border of the dermis. These experiments, then, also suggest that the most important source of fluid loss in a first degree burn is the superficial plexuses of small vessels in the papillary, and in the superficial part of the reticular layer of the dermis, and that, from here, fluid diffuses down throughout the whole-thickness of the skin.

In slices taken from fairly severe second degree burns made on the back of a hog, and in which the superficial vessels are destroyed by heat, the blue color is found to appear first, and in greatest intensity, along a wide line deep down in the dermis. From here the blue color spreads both up toward the papillary layer of the dermis and down into the subcutaneous tissue. These observations tend to confirm that the capillary beds associated with the deepest portions of hair follicles and the deep secreting portions of sweat glands are responsible for considerable fluid loss in this type of second degree burn.

If severe burns (20-30 seconds exposure) are produced on the abdomen of the hog, where the skin is much thinner than on the back, a deep blue color rapidly appears in the subcutaneous tissue.

The experiments with trypan blue tend to confirm the inferences drawn from the histologic studies, namely, that there are two capillary beds in the skin, and one in the subcutaneous tissue, which are the chief sites of fluid loss in burns of different intensities

#### SUMMARY AND CONCLUSIONS

1 Burns in many common laboratory animals do not give information applicable to human burns because the skins of these animals are different from the skin of man in the important respect that they are not designed to serve as organs for disseminating heat in hot weather and so lack papillae and the extensive set of superficial plexuses of small vessels that characterizes the skin of man and which, in conjunction with sweat glands, allows the skin of man to disseminate heat in hot weather

2 The skin of the hog is designed to allow that animal to disseminate heat in hot weather. It has papillae, abundant sweat glands and a reasonably extensive superficial blood supply

3 In young hogs, first degree and mild second degree burns show erythema and, to some extent, blister formation. Microscopically, these phenomena are seen to be due to changes in the superficial plexuses of small vessels that normally function in allowing the animal to lose heat. These vessels become dilated and congested to cause the erythema, and they leak plasma to cause the swelling and the blisters. The absence of this superficial blood supply explains why erythema and blisters cannot be reproduced in many common laboratory animals in burn experiments

4 In more severe second degree burns the skin surface tends to be white rather than red. Microscopically this is seen to be due to the superficial set of vessels being coagulated. Plasma loss in this type of burn originates from deeper capillaries. In this connection, it should be pointed out that the substance of the skin of both man and the hog is not evenly supplied with capillaries. We found that, in burns severe enough to seal off the superficial set, the next important set to become involved was that associated with the deepest portions of the hair follicles and the deep secreting portions of sweat glands. These become dilated and congested and leak plasma. The leaking plasma, moreover, escapes from the skin down into the subcutaneous tissue

5 In more severe burns a third great capillary bed is affected, that of the subcutaneous tissue

6 In the young hog information can be gained about the depth of a burn by pulling on the hairs in the burned area. If the burn is deep enough to involve the capillary beds associated with the deepest portions of hair follicles, there is edema of these. This loosens the attachment of the hairs so that they offer little resistance to being pulled free

7 The dilatation and congestion of both the smaller and larger blood vessels associated with the various types of burns studied in these experiments, together with the small hemorrhages that were not infrequently

observed, serves to emphasize that extensive burns would tend to abstract significant quantities of whole blood from active circulation in addition to the plasma that is lost by leaking away from the smaller vessels

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# EXPERIMENTAL STUDY OF THE TANNIC ACID TREATMENT OF BURNS WITH PARTICULAR REFERENCE TO ITS EFFECT ON LOCAL FLUID LOSS AND HEALING\*

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WHEN DAVIDSON<sup>1</sup> introduced the tannic acid method for treating burns he suggested that its efficacy was due to its precipitating proteins and so preventing absorption of toxins from the burn site. In the years that followed it became fairly generally accepted that the tannic acid treatment did indeed tend to diminish shock in burns. But the manner in which it accomplished this action became less certain as evidence accumulated to put increasing emphasis on fluid loss in and about the burn site as the cause of shock. It has, therefore, become of interest to determine whether tannic acid has an important function in tending to limit fluid loss in and about a burn and if so, how this is accomplished, and, furthermore, whether it acts in this manner with equal effectiveness in burns of all degrees or whether it could be expected to exert this action in only certain types of burns. The investigation herewith reported was undertaken to provide information on these points together with some others including the effects of tanning on healing.

## MATERIAL AND METHODS

Young hogs were used as experimental animals for reasons given in the preceding paper.<sup>2</sup> They were anesthetized by either subcutaneous or intravenous injections of ibatol, and burns were produced on their shaved skins either by holding the base of a 25 cc Erlenmeyer flask of boiler water against them for different numbers of seconds or by dipping their backs into the water at 80° C for different lengths of time. The burns were tanned by applying a coat of 10 per cent tannic acid to their surfaces, and then after this had dried, a coat of 10 per cent silver nitrate, and then, finally, after this had dried, successive coats of tannic acid during the next few hours. A complete débridement was performed on many burns before tanning, in our hands this entailed scraping the surface with a sharp scalpel in order to remove completely the epidermis from the dermis. Tissue for paraffin sections was obtained from burns of different ages caused by different lengths of time of exposure, and treated in different ways.

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Appreciation is due Doctors R P McCaffrey, G A L Ross and H F Whittaker for valuable assistance in carrying out the experiments.

OBSERVATIONS

*The Reluctance of Tanning Agents to Penetrate Epithelium*—In our experiments the epidermis of the skin proved to be a barrier to the penetration of tanning agents, even dead epidermis prevented the tannic acid from reaching and combining with the collagen of the dermis. To obtain satisfactory tans we were forced to remove the epidermis before applying the tanning agents and this we did by scraping it off with a sharp scalpel. The ability of dead epidermis to prevent the penetration of tanning agents is illustrated in Figure 1.

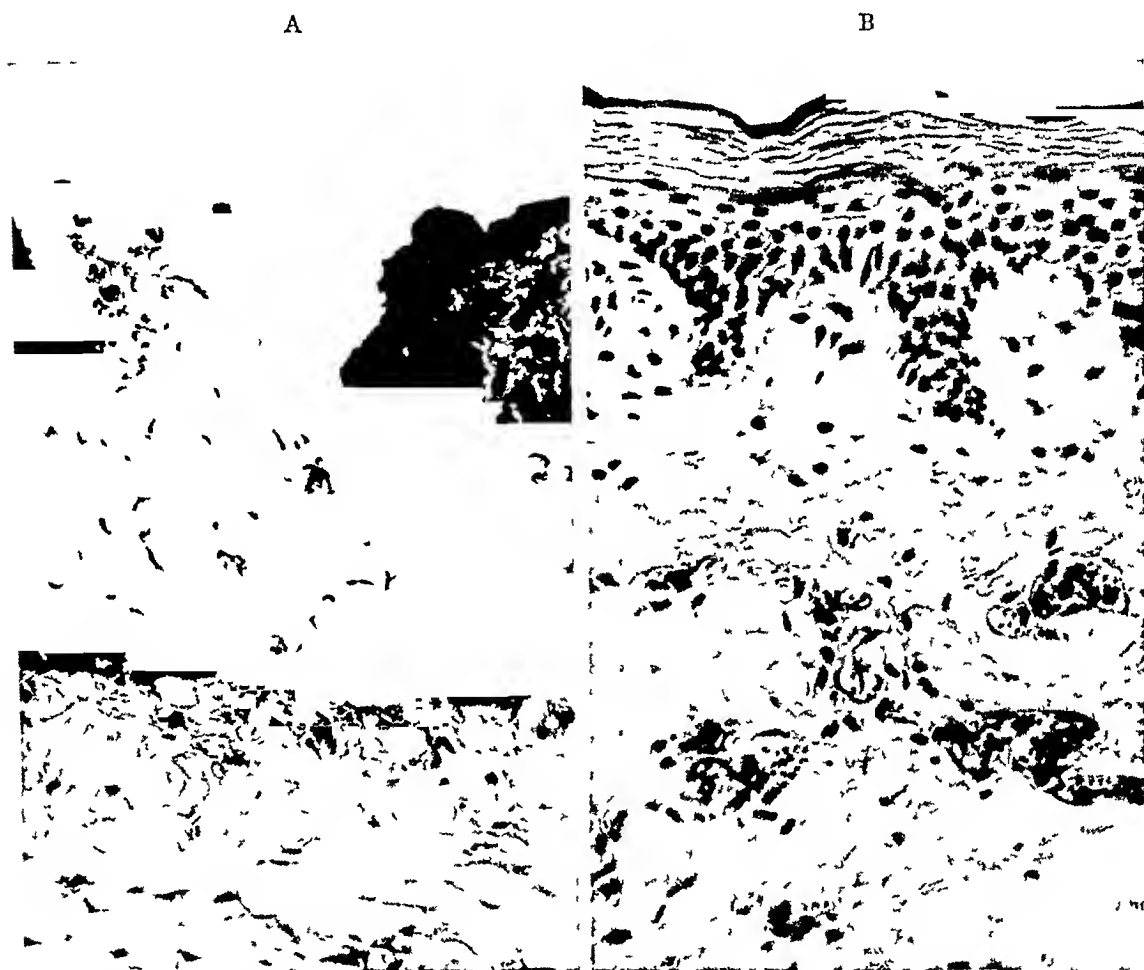


FIG 1—Low power photomicrographs of two different areas in a second degree burn produced on a young hog. Both areas were treated with tannic acid for about an hour and a half. In A, however, the epidermis was removed before tanning was begun, in B it was left intact. These sections show how dead epidermis prevents tannic acid from penetrating into the dermis. A is well tanned and B exhibits no tanning.

*Microscopic Features of Tanned Skin*—When tannic acid is applied in successive coats to a burned surface denuded of epidermis it penetrates remarkably evenly into the dermis, presumably by combining with the collagen in much the same fashion that it does in the manufacture of leather (Fig 1A). The depth to which tannic acid penetrates to form tanned dermis depends upon how long the denuded surface is kept wet with tannic acid. About one hour's exposure caused a penetration of about one-sixth of the thickness of the dermis, many hours exposure resulted in a penetration of a quarter to a third of the thickness of the dermis (Fig 2, A).

Frankly combining with the collagen of the superficial part of the dermis is, however, not the complete effect of tannic acid on the skin. It exerts a second effect, that of killing viable elements in the dermis for a considerable distance below the layer of dermis that is frankly tanned. The death of this second layer becomes apparent some hours after the tanning is finished and is evidenced by the gathering of leukocytes along a line some distance below the bottom of the frankly tanned layer. The line of leukocytes is well defined in 48 hours (Fig 2, A)

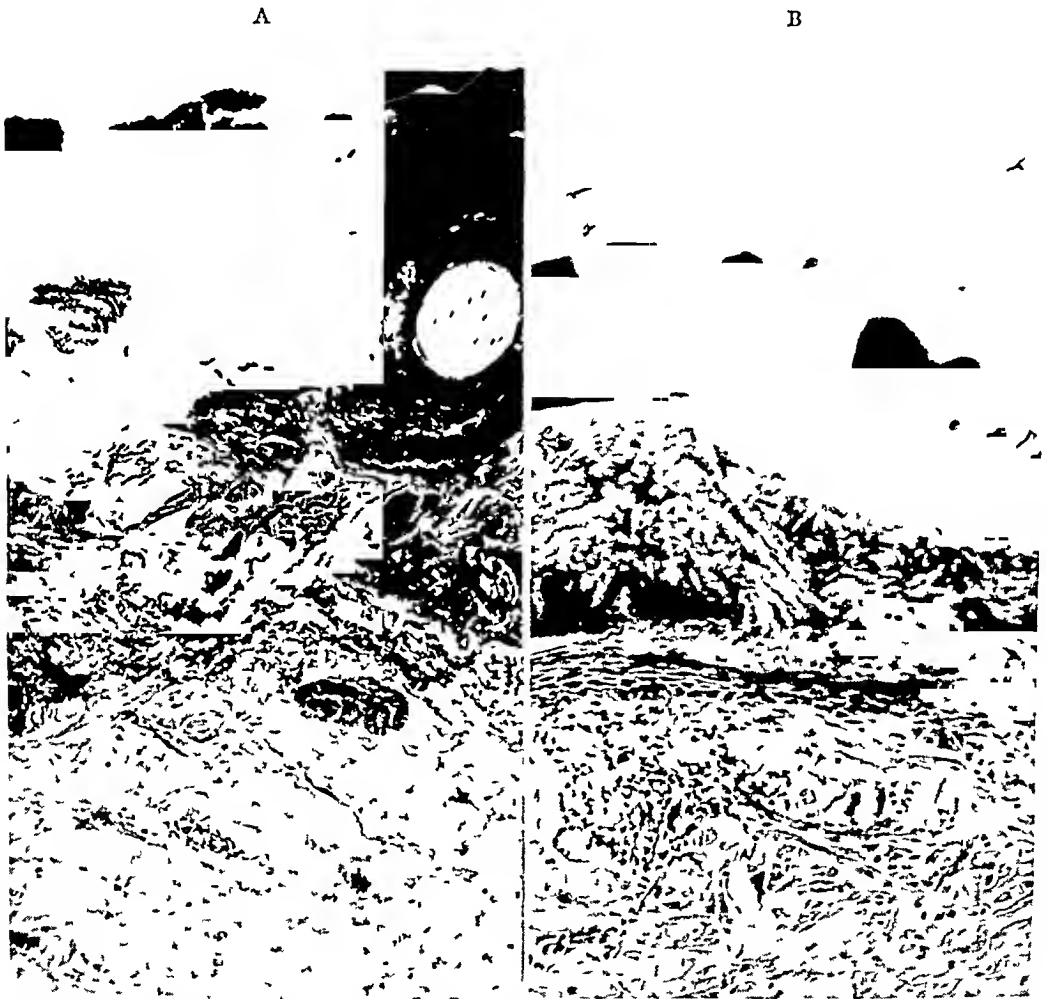


FIG 2—Low power photomicrographs of sections of tanned second degree burns

A illustrates very heavy tanning caused by keeping the burned surface wet with tannic acid for about eight hours. Below the frankly tanned dermis a second layer of dermis, killed, but not tanned, by the tannic acid can be seen. The lower border of this layer is marked by leukocytes. This tissue was obtained 48 hours after the burn was produced.

B illustrates a more lightly tanned burn. This section was obtained four days after the burn was produced, and it shows that new epidermis from hair follicles has grown along the line that is marked by leukocytes in A.

Tanning then, destroys a considerable thickness of dermis and the destroyed dermis consists of two parts, a more superficial layer that is frankly tanned and a deeper layer that is destroyed without being obviously tanned. Both these layers separate off in the eschar and the line of leukocytes seen in Figure 2 marks the line at which separation occurs. A tannic acid

## TANNIC ACID TREATMENT OF BURNS

eschar, then, contains two layers, an outer one that consists of frankly tanned dermis and a deeper one that consists of dermis killed, but not frankly tanned by the tannic acid (Fig 4)

*Why Tanning Could Be Expected to Diminish Fluid Loss in Certain Types of Burns*—In a previous paper<sup>2</sup> it was shown that there are three fairly distinct capillary beds from which fluid loss can occur in burns, and

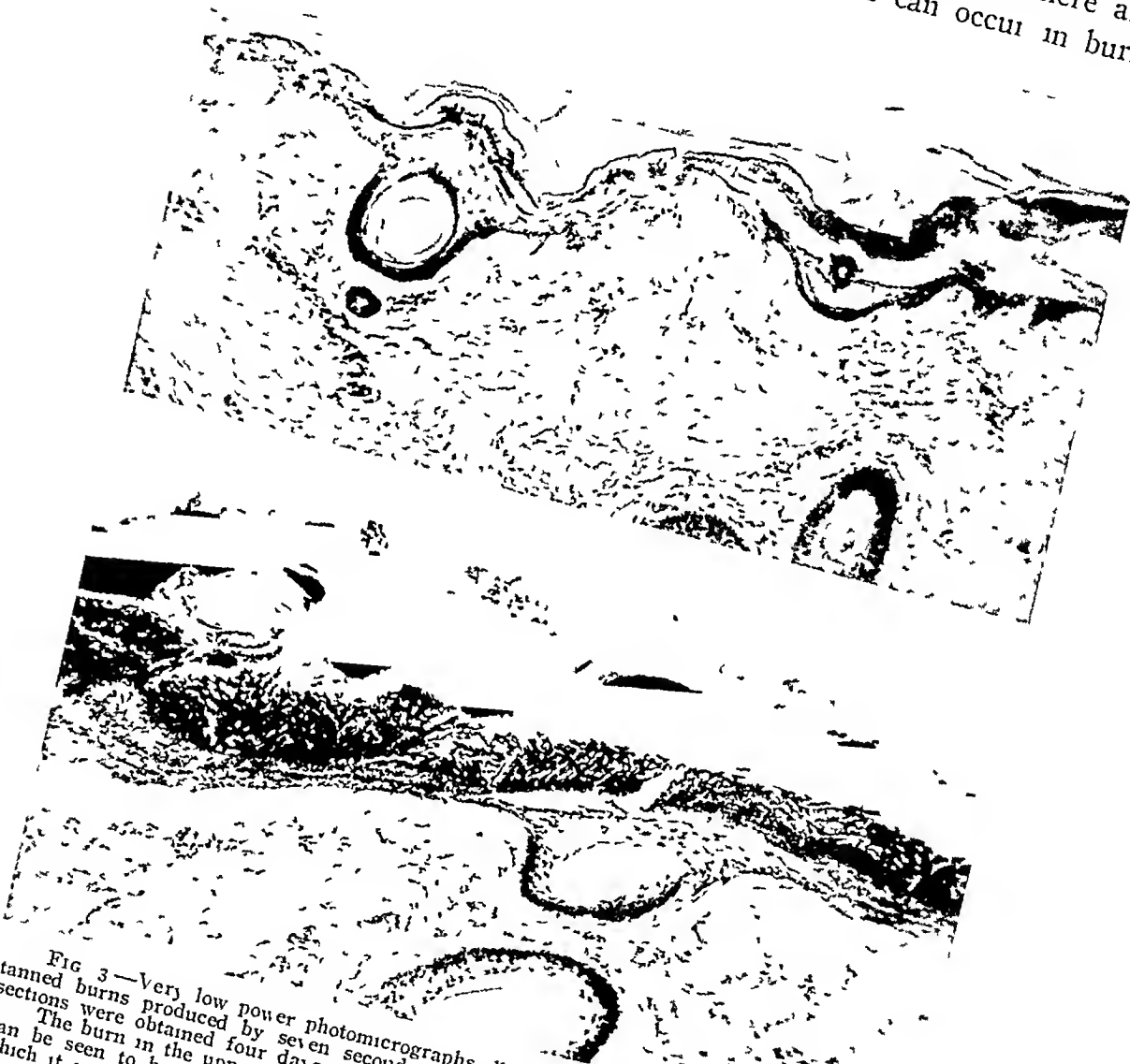


FIG 3—Very low power photomicrographs illustrating the healing of untanned and tanned burns produced by seven seconds exposure to a flask of boiling water. Both sections were obtained four days after the burns were produced. The burn in the upper photograph was not debrided or tanned, and a new epidermis can be seen to have grown out from hair follicles underneath the old dead epidermis which it is displacing. The burn in the lower photograph was debrided and tanned and a new epidermis can be seen growing out from hair follicles below the dermis that was killed by the tannic acid.

that each of these tends to be primarily involved in a certain type of burn. In first degree and in mild second degree burns it was shown that most fluid loss occurs from the superficial plexuses of vessels situated in the outer portion of the dermis. These vessels lie in the portion of the dermis that tends to be destroyed in effective tanning of the skin, hence, it could be

expected that tanning, by destroying the portion of the dermis that contains the leaking vessels, would tend to prevent fluid loss in this sort of burn.

In deeper burns, however, it has been shown<sup>2</sup> that fluid loss occurs chiefly from the capillaries associated with the deeper portions of the sweat glands and hair follicles, or even from the capillaries in the subcutaneous tissue. These capillary beds are too deeply situated to be incorporated into the layer of dermis that is reached and destroyed by the tannic acid, hence, tanning could not be expected to diminish fluid loss from these deeper burns in the same direct way that it does so in first and mild second degree burns.



FIG. 4—Very low power photomicrograph to show the state of healing in a tanned burn produced by seven seconds exposure to a flask of boiling water at four days. This illustrates very clearly how the epithelium grows out from the deeper portions of hair follicles to spread along under the eschar. Such separation of the eschar as has occurred is probably due to artefact.

*Experiments with Trypan Blue*—In these an attempt was made to compare the amount of plasma loss in tanned burns with that in untanned burns by performing experiments in animals given trypan blue intravenously and then estimating the amount of dye that leaked out in the treated and untreated sites. To do this two sets of comparable burns of all degrees were made by the flask method on a young hog and tanning was begun on one set immediately. One-half hour after the burns were produced the intravenous injection of a 1 per cent solution of trypan blue was begun and this was continued at a slow rate for from one to three hours and quantities up to 200 cc were given, although 100 cc was the usual amount given a 15-kilo hog. At the termination of the experiment slices were cut from the various burn sites and the amount and position of deep blue color on the cut surface was observed.

The results in first and mild second degree burns were not consistent, but in many instances the difference between the amount of trypan blue that leaked out in the skin in a tanned burn and an untanned one was impressive, there being far more trypan blue leakage in the untanned burns. It was observed, furthermore, that keeping the tanned skin dry assisted greatly in limiting the escape of trypan blue from the burn site, indeed, drying *denuded* dermis, even without tanning it, was very efficacious in preventing trypan blue leakage from a denuded first or mild second degree burn.



FIG. 5—Low power photomicrograph of a heavily tanned mild second degree burn 11 days after it was produced. This illustrates how heavy tanning necessitates the restoration of almost half the dermis and this occurs through the medium of granulation tissue which can be seen in this section to occupy almost the upper half of the dermis. Epithelization is complete.

In deeper burns, where the fluid loss occurs from deeply situated capillary beds, tanning was found to exert little or no effect on the amount of trypan blue that escaped at the burn site.

*Effects of Tanning on Healing*—In effective tanning, the superficial layer of the dermis is destroyed by the penetration of tannic acid. In the healing of a tanned burn a new skin surface forms along a line parallel to, and a short distance below, the bottom of the layer of dermis that is frankly tanned (Figs 3 and 4). In the healing of a tanned burn there must be,

therefore, (1) the formation of a new epidermis, and this develops from the epithelium of hair follicles (Figs 3 and 4), and (2) a restoration of the superficial layer of the dermis, and this forms through the medium of granulation tissue (Fig 5)

It is obvious, then, that tanning must necessarily slow the healing of a very superficial burn in which the complete thickness of the epidermis and the superficial layer of the dermis is not destroyed by the heat. But in our experiments this consideration proved to be more theoretical than practical. In burns produced by 4, 7, 10, 15, 20 and 30 seconds exposure to a flask of boiling water and allowed to heal for four days we found little difference in the state of epithelization in the untanned and tanned burns (Fig 3). This is because in all these burns (with the exception of a few areas in the four second burns) it was apparent at four days that the original epidermis had been destroyed by the heat and that healing demanded the regeneration of a new epidermis from hair follicles, and this, in our experience, formed as readily under a tan as it did under an eschar of dead untanned tissue. In the burns produced by 4 and 7 seconds exposure, epithelization from hair follicles was almost complete in four days time in both the tanned and untanned burns. In the 10-, 15- and 20-second burns there was considerable cellular activity in the hair follicles and some prongs of epithelium were seen extending out along the line of separation between dead and living tissue. In the 30-second burns all the epithelium in most of the hair follicles was dead and there was new growth in only a few of them.

In untanned mild to moderate second degree burns we observed that persistence of dead epidermis over the burn made considerable difference in the nature of the healing process. If the epidermis was detached and the dermis exposed to air, the superficial layer of the dermis dried and subsequently separated off in much the same manner as a tannic acid eschar with epithelium having formed below it. When the dead epidermis remained adherent to the dermis, however, it acted in a protective fashion and if the burn was not too severe it tended to preserve the superficial portion of the dermis so that epithelium from hair follicles could grow along under the old epidermis to take up its position on the original dermis.

To sum up. Our experiments gave little indication that tanning slows the process of epithelization except in very superficial burns. In the less severe second degree burns, however, tanning kills more dermis than would otherwise die (unless it is exposed and becomes dry), therefore, tanning demands a more extensive regeneration of dermis than would otherwise be necessary in this sort of burn.

#### SUMMARY AND CONCLUSIONS

1. In the young hog, either living or dead epidermis prevents the absorption of tannic acid into the dermis of the skin.
2. When dead epidermis is thoroughly removed from the surface of a burn, tannic acid penetrates in a remarkably even fashion into the dermis.

3 In our experiments, the depth to which tannic acid penetrated depended on how long it was applied, and tans that ranged from about one-sixth to almost one-half the thickness of the dermis were obtained by different lengths of treatment

4 The application of tannic acid not only destroys the superficial layer of dermis with which it combines to form tanned skin, it also destroys a layer of dermis below that which is frankly tanned. The deep border of this second layer is usually soon marked by a line of leukocytes and it is along this line that reepithelization occurs in healing

5 The superficial layer of dermis destroyed in efficient tanning contains most of the capillaries and venules of the superficial plexuses of vessels that in both man and the hog are normally concerned in temperature regulations and from which most of the fluid loss occurs in first and in the milder forms of second degree burns. By directly destroying the dermis containing these vessels it could be expected that tanning would tend to diminish fluid loss from this sort of burn

6 Some experiments with trypan blue indicated that tanning diminished leakage in this type of burn, but other experiments were not convincing. When denuded tanned dermis was allowed to dry, however, experiments with trypan blue showed very convincingly that plasma leakage in this type of burn was greatly diminished by the combined procedure

7 Experiments with trypan blue gave no indication that tanning materially affects plasma loss in deeper burns in which the superficial plexuses are mostly sealed-off by the heat and leakage is primarily from the capillaries associated with the bulbs of the hair follicles and the deep secreting portions of the sweat glands or the capillaries of the subcutaneous tissue, all of which are deep to the dermis destroyed by the tannic acid

8 In very superficial burns where the epidermis is not completely destroyed the tannic acid treatment slows healing slightly because effective tanning always demands the formation of a new epidermis from hair follicles and a regeneration of the layer of dermis destroyed by the tannic acid. But in any but the most superficial burns the whole epidermis is destroyed by the heat and a new epidermis must form in any event, and this forms as readily under a tan as not. Hence, in any but very superficial burns tanning does not materially slow epithelization although it frequently demands the restoration of more dermis than might otherwise be necessary

9 If these experiments have any clinical application it is, perhaps, that if the tannic acid method of treating burns has a use it is in the sort of burn in which most of the fluid loss occurs from the superficial plexuses of vessels that are normally concerned in temperature regulation, and that to be effective in preventing fluid loss from these the tan should be kept dry. The work provides no evidence to suggest that the tannic acid treatment would be equally efficacious in the more severe second degree burns or in third degree



burns where plasma loss occurs primarily from capillary beds out of reach of the tan

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# REFRIGERATION IN CLINICAL SURGERY\*

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DURING RECENT YEARS refrigeration has been employed increasingly in the surgical treatment of gangienous limbs. Its value remains in dispute chiefly because of a lack of satisfactory information regarding the effect of cooling on the healing of the wounds and on the progress of infection.

Enough general knowledge pertaining to the effect of cold has accumulated to warrant its analysis to determine, if possible, the advantages and disadvantages which might be expected to follow from prolonged cooling of tissues. Such knowledge should serve as a basis for the evaluation of measures involving the use of refrigeration in clinical surgery. Because the tourniquet has usually been employed in conjunction with refrigeration in the treatment of patients, any discussion of the merits and harmful effects of refrigeration preferably should include a consideration of the effects of the tourniquet. In this paper a discussion of the effects of cooling and of the effects of asphyxia produced by the application of a tourniquet will be followed by the presentation of cases in which a form of treatment in harmony with the implications of established physiologic principles has been employed.

## THE EFFECT OF REFRIGERATION ON TISSUES

Within physiologic limits the velocity of most biologic processes varies directly with the temperature. At temperatures close to freezing there is almost complete cessation of cellular activity. Another pertinent observation is that conduction in a nerve trunk fails at or below certain critical temperature levels ( $25^{\circ}$  to  $30^{\circ}$  C in warm blooded animals),<sup>1</sup> thus accounting for the phenomenon of refrigeration anesthesia.

The changes which occur during and following the prolonged cooling of an extremity are of particular interest. While the tissues are cooled they are anesthetic and their metabolism is greatly diminished. After exposure to cold ( $3^{\circ}$  to  $4^{\circ}$  C for 24 to 96 hours) rats' tails show marked degeneration of nerves and muscles in the cooled areas.<sup>2</sup> The dog's forelimb, after immersion in cold water, exhibits edema and paralysis of the involved member, and these signs are followed by degeneration of the cooled peripheral nerves.<sup>3</sup> Similar, but more marked, changes are seen sometimes in shipwrecked sailors on exposure to cold and wet for varying periods. Such individuals may develop long-standing vascular and neurotrophic disturbances, and, in the most severe cases, gangrene of the feet.<sup>4</sup> Thus, the magnitude of tissue changes resulting from exposure to cold may be considerable. Although

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\* The experimental basis for this report was made possible by a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the Washington University School of Medicine, St Louis, Mo

low temperatures may produce some injury by a direct effect upon living cells, there is rather general agreement that cold causes ischemia of the cooled part, and that lack of oxygen is responsible for most of the damage. During cooling there is an accumulation of tissue metabolites, which, after the cooling agent is removed, causes reactive hyperemia and other changes similar to those following the removal of a tourniquet (*qv*) although as a rule the changes are not profound enough to produce systemic effects.

Since normal tissues are damaged by cooling, the cells in areas undergoing reparative and inflammatory changes also would be expected to be affected adversely. Inhibition of healing of wounds during refrigeration has been shown to occur in the experimental animal by Large and Heinbecker.<sup>5</sup> Their studies also demonstrated that following the cooling period wound healing was delayed, the degree of delay being roughly proportional to the duration of the cooling period. Degenerative changes were shown to occur in the nerves of cooled extremities, and these are considered responsible, in part at least, for the delay in the healing of wounds long after the actual exposure of the tissues to cold has ended.

Brooks and Duncan,<sup>6</sup> in carefully controlled experiments, observed that the inflammatory reaction to intradermal injections of bacteria and of oil of turpentine was inhibited during the cooling period. Following refrigeration the inflammatory reaction in injected areas was slightly greater than in the controls, with possibly some increase in actual necrosis. Bruneau and Heinbecker<sup>7</sup> found that during the cooling period no inflammatory response developed to *Streptococcus hemolyticus* injected subcutaneously and into joints of dogs' limbs, while after refrigeration the tissues exhibited a decrease in growth restricting action toward the bacterial organisms, the inflammatory reaction being more marked than in the controls. Large and Heinbecker<sup>5</sup> studied the healing of wounds treated by delayed suture after 24- or 48-hour cooling periods, and found that the refrigerated wounds showed a much higher incidence of gross infection, with suppuration, than did the uncooled controls.

#### THE EFFECT OF A TOURNIQUET

The tissues distal to the area of constriction are ischemic, and if rendered so for a sufficient time, undergo degeneration. Lewis<sup>8</sup> has shown that muscle fibers fail to recover their ability to contract when deprived of their blood supply for 6 to 8 hours, nerves die after 12 to 20 hours, the skin after 24 to 48 hours of ischemia. The tourniquet itself, if narrow and tight, may, by direct pressure on nerves, cause temporary paralysis. During the period of constriction, metabolites causing vasodilation accumulate, so that after the tourniquet is released, a period of reactive hyperemia ensues. If the mass of tissue distal to the tourniquet is large, release of the constriction may result in shock and even in death.

The effect of a tourniquet on the progress of infection varies with the duration of the period of ischemia. The cessation of blood flow presages

an interruption of the inflammatory reaction, which is inimical to the controlling of the infection following removal of the tourniquet. However, if a tourniquet be applied tightly enough to a limb proximal to a gangrenous or infected area, the obliteration of vascular and lymphatic channels at the level of constriction will prevent absorption of toxins and bacteria from the involved region into the general circulation. This beneficial effect will continue as long as the tourniquet is in place, unless the disease process is able to spread above the level of constriction by direct continuity of tissue.

#### EFFECT OF A TOURNIQUET AND REFRIGERATION USED SIMULTANEOUSLY

The survival time of a tightly constricted limb is prolonged greatly by refrigeration of the part. This was shown experimentally by Allen,<sup>9</sup> and demonstrated conclusively, to be true by Brooks and Duncan,<sup>10</sup> who found that rats' tails rendered completely ischemic in a pressure apparatus lived many hours longer without the subsequent development of gangrene when exposed to temperatures of 1° to 15° C than did those at room temperatures. The other effects of these agents used together can be predicted from the known changes following their individual or separate applications.

In summary, then

a The benefits of refrigerating an extremity include loss of sensation and diminution of absorption of noxious agents from the cooled area, while the disadvantages lie in a subsequent delay in wound healing, a greater risk of infection, and a varying degree of actual damage to refrigerated tissues left *in situ*.

b The benefits of the application of a tourniquet to a limb refrigerated *above* the proposed level of amputation include anesthesia and the elimination of absorption of noxious agents, with increased duration of viability of the completely ischemic tissues, while the ill effects, again, include delayed wound healing, greater risk of infection, and actual tissue damage to the refrigerated stump.

c The benefits of refrigeration with the application of a tourniquet *below* the proposed level of amputation of a limb, as in the other instances, include loss of sensation and elimination of absorption of noxious agents from the part, the further advantage of eliminating interference with wound healing and the spread of infection also is assured.

#### CLINICAL APPLICATIONS

The management of critically ill patients with gangrenous extremities frequently involves the control of toxemia, of infection, of anemia and of derangements in metabolism. If absorption of toxins from the involved limb can be prevented for a time, the patient's general condition can be improved enough so that operation may be performed with much less risk. This can be accomplished most simply by a tourniquet about the limb above the involved area, but below the level of proposed amputation. Such a plan was

followed not infrequently during the last war, and, more recently, Maxeimer (1941)<sup>11</sup> reported the successful use of "temporary tourniquet amputation" in 12 cases. Adolph<sup>12</sup> advocated a similar method. The results obtained, in general, were satisfactory, but the patients had severe pain until the tourniquet produced anesthesia, and occasionally infection developed above the level of constriction.

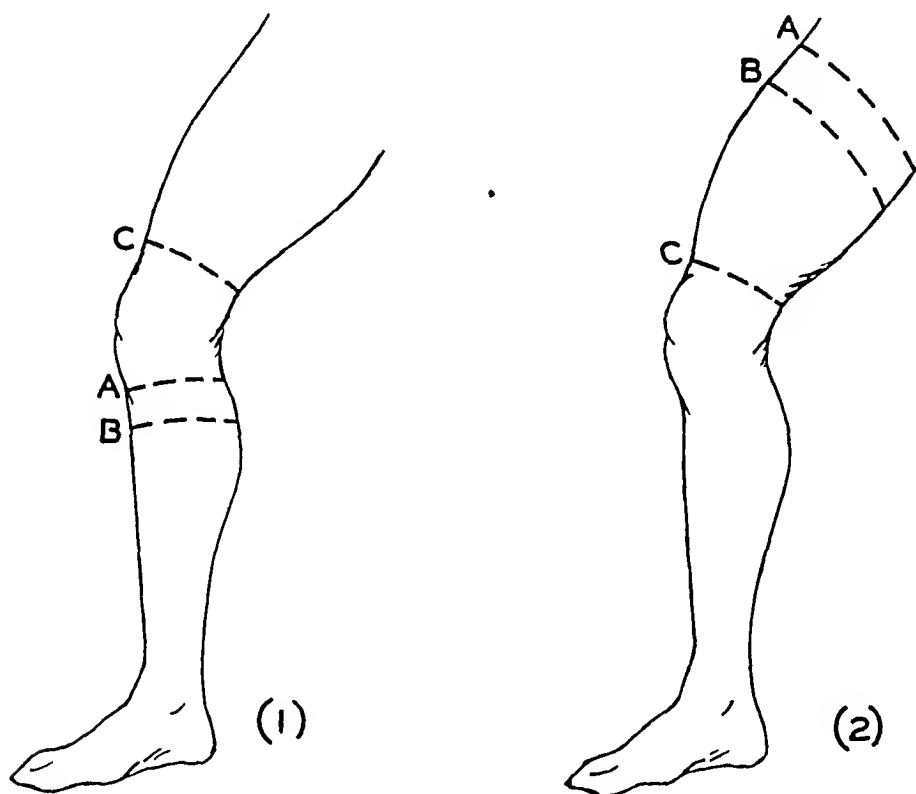


FIG. 1.—Diagrams of methods of use of refrigeration and the tourniquet before operation. A Level of refrigeration. B Site of application of tourniquet. C Level of amputation.

(1) Diagram showing the advocated level of refrigeration, A, and the site of amputation, C. Note that the distance AC is considerable.

(2) Diagram showing the method of refrigeration anesthesia as employed by Allen, and others. Note that the large mass of refrigerated tissue AC is not excised.

Allen, in certain experiments,<sup>10</sup> found that a tourniquet could be applied painlessly, if the limb were refrigerated first. He suggested the use of refrigeration together with a tourniquet in the preparation of poor-risk patients with gangrenous feet for amputation, and introduced the clinical use of refrigeration anesthesia for such operations.<sup>14</sup> The type of procedure advocated by him, and his coworkers,<sup>15</sup> is indicated in Figure 1. The disadvantage of this method appears to lie in the fact that much of the cooled, and, therefore, damaged tissue is not excised. It is felt preferable that all refrigerated tissue should be removed at operation. This can be done by applying the tourniquet and the cold distal to the level of amputation as indicated in Figure 1.

## ILLUSTRATIVE CASES

**Case 1**—H H, a 54-year-old white female, known to have diabetes mellitus, was admitted to the Barnes Hospital, April 10, 1943, with a three-month history of spreading infection of the right foot. Examination showed a toxic, drowsy, but rational female, who seemed critically ill. The temperature was 39.6° C. The right 5th toe was absent, and there was a large, foul, necrotic, sloughing ulcer on the lateral aspect of this foot, from which thick pus could be expressed. Induration and swelling were present up to the ankle. There were no palpable arterial pulsations in either foot, but both popliteal pulses could be felt. Laboratory findings included Hb, 42 per cent, W B C 17,000,

## BARNES HOSPITAL

History No 105557

Name SEKETA, JOSEPH J.

Admitted 5-22-43

Ward 1200

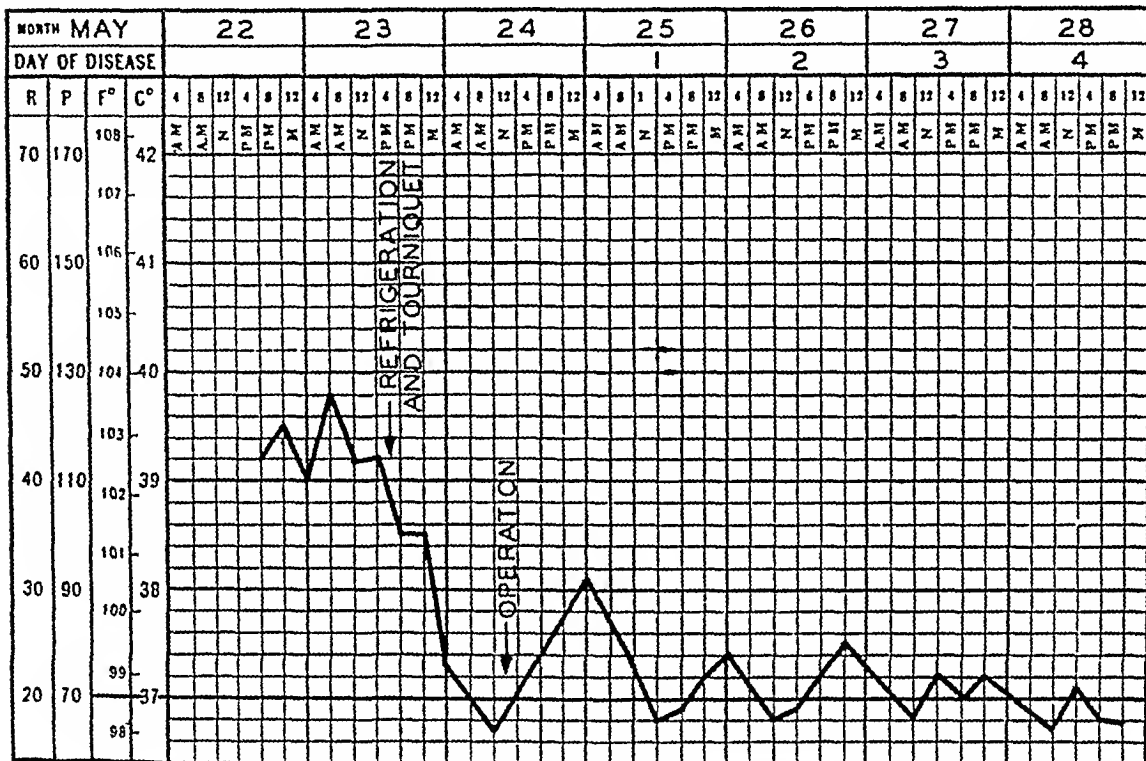


CHART 1—Case 2 Temperature chart Note the failure of response to intravenous sodium sulfadiazine and general supportive measures during the first 24 hours of hospitalization, and the marked improvement following refrigeration and the application of a tourniquet

urine, one plus sugar, numerous W B C , blood sugar 324 mg per cent, blood N P N 13 mg per cent Insulin, whole blood, fluids and sulfadiazine were given In the evening of the day of admission, ice bags were placed about the right leg and foot almost up to knee level and two hours later a tourniquet was applied to the leg just below the knee The patient gradually became more comfortable, and within six hours the temperature had fallen to normal Twelve hours after refrigeration had been instituted, a right midthigh amputation was performed, under spinal anesthesia, without release of the tourniquet The wound was closed with drainage, and the drain was removed after 24 hours The postoperative course was uneventful, the wound healed *per primam* The patient was discharged from the hospital, May 8, 1943, 28 days after admission, in good condition

Case 2—J J S, a 48-year-old white male, was admitted to the Barnes Hospital, May 22, 1943, and stated that he had had pain in the legs and feet during exercise or in cold weather for six years. A month and a half prior to admission, an area of infection developed about the right great toe, this was treated conservatively, but gangrene of

the toe developed and it was amputated with closure of the stump, elsewhere, eight days prior to admission. Three days before entry the foot became painful, swollen and blue. Pain was so severe that frequent injections of morphine failed to give relief.

Examination showed a critically ill, middle-aged male who frequently dropped off to sleep, his memory was hazy and he was obviously quite toxic. The temperature record is shown in Chart 1. The distal portion of the right foot was gangrenous, and the remainder of the foot up to the ankle swollen, puffv and extremely tender. No arterial pulsations could be felt in the foot, but the popliteal pulse was palpable. Laboratory findings included a W B C of 30,000, and a blood culture was positive for *Streptococcus hemolyticus*.

The patient was given fluids, intravenous sodium, sulfadiazine, and gas bacillus antitoxin, without improvement. Therefore, the day after admission, ice bags were packed around the right foot and leg to just below the knee, and when sensation disappeared, a tourniquet was applied to the leg. Improvement in the general condition was dramatic (see Chart 1), and 24 hours later a circular supracondylar amputation was performed under spinal anesthesia. The wound was closed without drainage. Healing *per primam* followed, and the patient was discharged from the hospital, June 8, 1943, 17 days after admission, in good health.

Histologic study of the amputated tissues confirmed the clinical diagnosis of Buerger's disease, with gangrene of the foot.

**Case 3**—M. H., a 19-year-old white female, was admitted to the Barnes Hospital May 26, 1943. She had been knocked off a motorcycle three days before, and a compound fracture of the right ankle sustained, this was treated elsewhere. Spreading infection soon appeared, and the patient was referred to Barnes Hospital for further treatment.

Examination showed an acutely ill, toxic young girl complaining of severe pain in the right leg. The temperature was 38° C. There was evidence of an unredueed fracture of the right ankle, on the lateral side of which was a necrotic, foul-smelling wound from which bubbles of gas could be expressed. The entire right foot and leg were swollen, exquisitely tender, and crepitant, and gas could be felt in the subcutaneous tissues of the thigh as well. Roentgenograms confirmed the diagnosis of gas gangrene.

Large doses of polyvalent gas bacillus antitoxin were administered, the leg was packed in ice up to the level of the knee, and a tourniquet applied. The symptoms rapidly subsided, and, four hours later, under general anesthesia (eyelopropane), a guillotine supracondylar amputation was performed, and several incisions were made over the involved portions of the right thigh. The wounds were left open, and they were irrigated frequently through tubes placed therein. Healing was slow but satisfactory. The patient was discharged from the hospital, July 3, 1943, with all wounds healed.

**Case 4**—J. M. L., a 50-year-old white female, was admitted to the Barnes Hospital, November 13, 1943, for removal of an acoustic neuroma on the right side. A meningioma was removed through a cerebellar craniotomy on November 16, 1943. During convalescence the patient, who also suffered from rheumatic heart disease with auricular fibrillation, released an embolus which lodged at the bifurcation of the aorta, and although a large embolus was removed from the left femoral and iliac vessels, November 27, 1943, both legs had to be amputated subsequently just above the knee. On December 4, 1943, a right supracondylar amputation was performed. The patient then developed fever of 39.8° C, and this was thought due to infection in the gangrenous left foot. Accordingly, December 6, 1943, ice packs were applied to the left leg up to the knee, and after two hours a tourniquet applied below the knee. The temperature immediately fell to normal, and 18 hours later, a left supracondylar amputation was performed under general anesthesia (ethylene). The wound was closed without drainage. Post-operative progress was slow, but satisfactory. A slight degree of muscle breakdown occurred and drained out through a small sinus track. This had not healed completely

when the patient left the hospital, January 19, 1944, but did so in about two weeks thereafter

**Case 5**—A C, a 61-year-old colored male, was admitted to St Louis Homer Phillips Hospital December 4, 1943. He had fallen out of a second story window one hour previously and was unconscious for some time. Examination showed a deep laceration of the forehead and a severe injury to the right eye, which subsequently developed traumatic cataract. As the patient became more alert, he began to complain of pain in the left leg and foot. The latter was cold, insensitive and paralyzed, and the left popliteal and tibial pulsations were absent. There was a small chip-fracture of the lateral condyle of the left femur.

It was thought that thrombosis in an arteriosclerotic popliteal artery had occurred following direct injury. There was no evidence of an hematoma in the popliteal space. Conservative therapy was tried, but was unsuccessful. Gangrene of the left foot and lower leg gradually developed. There was severe pain and fever as high as  $41^{\circ}$  C. Accordingly, December 17, 1943, the left leg and foot were packed in ice and a tourniquet applied below the knee. Improvement was dramatic, the temperature shortly falling to  $37.6^{\circ}$  C. Twenty-four hours later, under spinal anesthesia, a mid thigh amputation was performed. The wound was closed over a small rubber dam drain, around which there exuded a small amount of serous fluid which stopped when the drain was removed 48 hours after operation. The wound healed *per primam*. The patient had some fever after operation, but this disappeared when sulfathiazole, which was being administered prophylactically, was discontinued. His subsequent course, as far as the amputated limb was concerned, was entirely satisfactory, although he was kept in the hospital until February 9, 1944, for treatment of his injured eye. Histologic study of the amputated leg confirmed the clinical diagnosis of thrombosis in a sclerotic popliteal artery, with resultant gangrene.

**Case 6**—C B, a colored female, age 57, was admitted to the St Louis Homer Phillips Hospital December 10, 1943. She had had a partial amputation of both feet for frostbite nine months previously, and had been living in an unheated basement in the interim. Her present complaint was increasing pain in both stumps for some three weeks, following repeated exposures to cold. Examination showed moist gangrene of both stumps, with swelling and tenderness to midleg level on both sides. Conservative treatment was attempted, but the gangrene extended and infection became more marked. The temperature ranged around  $39^{\circ}$  C occasionally reaching  $40.6^{\circ}$  C. Since both popliteal pulsations were good, it was decided to amputate below the knees. On January 10, 1944, both stumps were refrigerated, and tourniquets applied just above the line of demarcation at the ankles. The temperature fell rapidly to normal, and next day bilateral midleg amputations were performed under spinal anesthesia. The wounds were closed, with drainage. There was some sloughing of the skin margins of the lateral aspects of both wounds, and complete healing had not occurred after one month, but the patient's general condition was at all times satisfactory after operation. It was felt that the delayed healing in this case may have been associated with amputation too close to the refrigerated areas.

**COMMENT**—Each of the six cases presented had gangrene of one or both feet associated with infection and toxemia. In one instance (Case 2) there was septicemia. The basis for the gangrenous process, as determined by histologic study, was different in each of the cases—diabetic arteriosclerosis, thrombo-angitis obliterans, spreading gas bacillus infection, peripheral embolism, popliteal thrombosis and frostbite being found. The patients were operated upon without mortality and without encountering difficulty with the subsequent wound healing. It is felt justifiable, therefore, to



advocate the use of the method to others, in order that through wider experience its real merits may be determined

The details of the procedure used are not complicated. In all but the last case, ice bags were applied nearly up to the knee (Fig 1) and the tourniquet placed below the knee two to four hours later, after anesthesia had been obtained. When the patient's general condition warranted it, usually after 24 hours, amputation was performed above the knee, using inhalation or spinal anesthesia. Because it is known that living tissues will conduct cold fairly efficiently,<sup>16</sup> and for other reasons already considered, it is important that the amputation be carried out well above the refrigerated area. None of the patients herein reported suffered from shock during or after the operation, an advantage stressed by the proponents of refrigeration anesthesia.

The small number of cases treated by this method does not warrant any sweeping claims. However, refrigeration was not used in any case unless the patient's condition was so poor, due to severe infection and absorption from the gangrenous part, that the ordinary methods of treatment seemed dangerous. Such cases previously have been treated by guillotine amputation, followed by elective amputation at a higher level at a later date. By the method herein employed the necessity for two operations has been obviated.

#### SUMMARY AND CONCLUSIONS

Refrigeration of an extremity abolishes pain and lessens the blood and lymph flow. When such refrigeration is followed by, and combined with, the application of a tight tourniquet, absorption of toxic products from an infected gangrenous extremity is, for all practical purposes, eliminated.

Because refrigeration tends to delay wound healing and decreases the power of resistance of tissues to bacterial invasion, the prolonged cooling of tissues to be preserved is not advocated. It is recommended that necessary amputations be carried out above the level of cooling.

Because a patient's general condition can be improved so greatly, during the combined use of cold and the tourniquet, by ordinary restorative measures, it is unnecessary to avoid the use of inhalation or spinal anesthesia for amputation.

Six illustrative cases cared for in accordance with the above principles are reported.

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# EFFECTS OF COOLING ON EXPERIMENTALLY INFECTED TISSUES<sup>1</sup>

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THE EFFECTS OF REDUCED TEMPERATURES on tissue survival under anoxia and on tissue resistance to infection have been studied in several recent investigations. Allen,<sup>1</sup> and Brooks and Duncan,<sup>2</sup> showed that cooling greatly prolongs the life of tissues deprived of their blood supply. The experiments of Brooks and Duncan<sup>1</sup> also have demonstrated, conclusively, that the local application of cold without interference with the blood supply prevents the development of the normal tissue response to bacterial organisms (*Staphylococcus aureus*) and to chemical irritants (turpentine) injected intracutaneously, and that the appearance of the classical signs of inflammation rapidly follows the return of the affected part to a normal environmental temperature.

In this communication are reported the results of an investigation to determine the effects of reduced temperatures on both the local tissue response and the organisms responsible for it, and to determine the eventual course of a local infection as altered by a temporary period of cooling.

## EXPERIMENTAL PROCEDURE

A concentrated suspension of *Streptococcus hemolyticus* in broth was used to produce a localized infection. The suspension was obtained from 18-hour cultures, and bacterial counts showed its concentration to vary within the range of  $10^8$  to  $10^9$  in all specimens.

Mongrel dogs weighing from four to eight kilos were used as experimental animals. After the hair was removed from one of the forelegs, 0.5 cc of the suspension was injected into the wrist joint or into the subcutaneous tissues above the wrist. The inoculated limbs were then cooled to six degrees C for various lengths of time. Cooling was effected by immersing the limb to a level well above the elbow in a constant temperature bath provided by a commercial cooler. The dogs were immobilized in canvas hammocks and the affected limb in the cooler was made secure by a tie placed well below the wrist. This insured the uninterrupted cooling of the limb and did not interfere with the blood supply to the inoculated area. No protective substances were applied to the skin, and food and water were not withheld from the animals during the course of the experiment. The control animals

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\*The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the office of Scientific Research and Development and Washington University, St Louis, Mo

were injected in a similar fashion and were placed in cages at room temperature for equivalent periods of time, no effort being made to immobilize the inoculated limb. These experiments were carried out for periods ranging from 24 to 96 hours. Each experiment was performed on two groups of six dogs. In the first group, the gross and microscopic structure of the lesions was studied, and bacterial counts were made from samples of the exudate. This method of securing material for counts was found to be in-

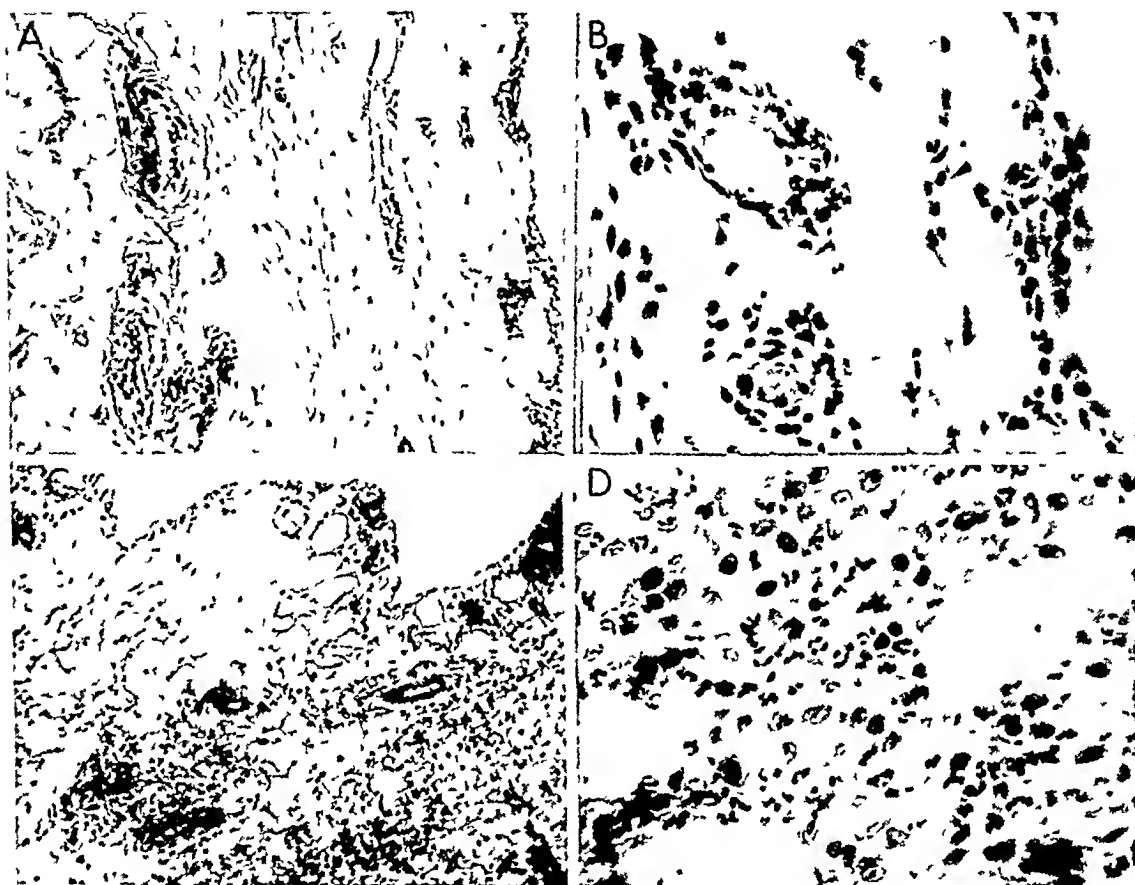


PLATE I—A Photomicrograph ( $\times 135$ ) of the synovial membrane of a dog's wrist joint inoculated with "*Streptococcus hemolyticus*" and cooled at  $6^{\circ}\text{C}$  for 48 hours.  
B Photomicrograph ( $\times 425$ ) Same as A, to show more clearly the vascular congestion and minimal degree of leukocytic infiltration.  
C Photomicrograph ( $\times 135$ ) of the synovial membrane of a dog's wrist joint inoculated with "*Streptococcus hemolyticus*" and maintained at room temperature for 48 hours.  
D Photomicrograph ( $\times 570$ ) Same as C, to show more clearly the slight degree of acute inflammatory response exhibited in the joint synovial membrane of the control dog.

accurate—so that a second group of animals was prepared in which at the completion of the experimental cooling, the tissues at the site of inoculation were excised "*en bloc*," care being taken that the excision extend well out into normal tissue. These specimens were then homogenized and the total number of bacteria per sample determined. The controls were carried out similarly in two groups of six animals for each experiment.

All bacterial counts were determined by dilutions in broth poured over blood agar plates and are expressed in number of bacteria per cubic centimeter. Contamination was very infrequent, and the organisms recovered were invariably identified as "*Streptococcus hemolyticus*."

## EXPERIMENTAL RESULTS

The effect of local cooling on infected subcutaneous tissues was studied for periods of time varying from 24 to 96 hours

In a first experiment dogs were inoculated subcutaneously with 0.5 cc of the bacterial suspension. In one group the limbs were cooled for 48 hours immediately following the injection, and the animals were then sacrificed. The other group was left at room temperature for the same period of time before being studied

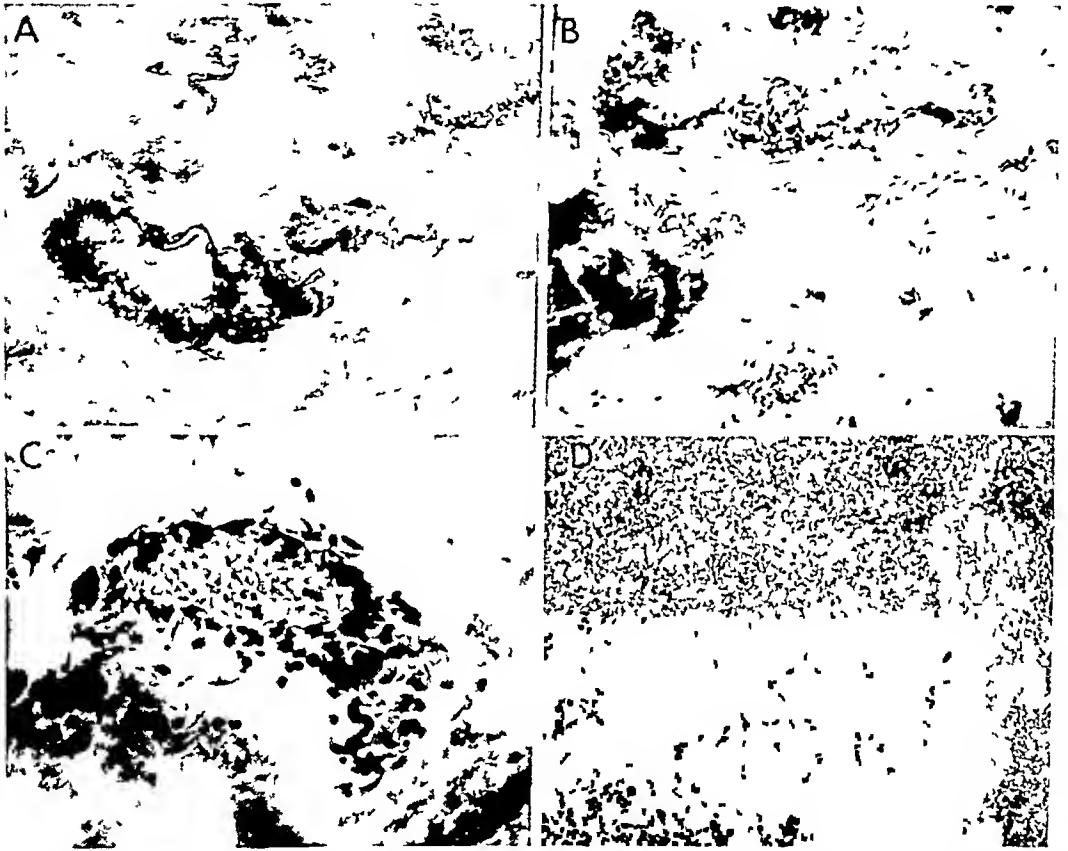


PLATE II—A Photomicrograph ( $\times 50$ ) of the subcutaneous tissue of a dog's limb at the site of inoculation after cooling 48 hours at  $0^{\circ}\text{C}$ . Note the presence of vascular congestion and edema without appreciable leukocytic infiltration around the dark ring of bacteria embedded in the tissues.

B Photomicrograph ( $\times 135$ ) from the same area as A to show the relatively acellular edema and minimal diapedesis.

C Photomicrograph ( $\times 570$ ) from the same area as A showing a distended capillary near a cluster of bacteria (lower part of picture). Note the absence of tissue reaction to the bacteria.

D Photomicrograph ( $\times 50$ ) of the subcutaneous tissues of a dog's leg at the site of inoculation with "*Streptococcus hemolyticus*" after 48 hours at room temperature. Note the marked acute inflammatory reaction.

In the limbs that had been subjected to cooling there was no external evidence of inflammation at the site of inoculation. Local anesthesia and local loss of motor function were noted in all animals. At autopsy, on gross examination, diffuse edema, though of varying degree, was found to be present in all cases throughout the area that had been immersed and to involve mostly the subcutaneous layer. The edematous tissue had a greyish-blue color and a viscid, gelatinous consistency. Around the site of injection, these greyish tissues assumed a faint pinkish color. Closer examination of

the area showed a fine reddish reticulum suggestive of dilated blood vessels. Gross extravasation of blood was not observed.

Even away from the site of inoculation, there was microscopic evidence of marked vascular congestion and edema. Around the congested capillaries one could see a few polymorphonuclear and red blood cells. These findings were also observed in the subcutaneous tissues of animals that had been submitted to cooling without any bacterial inoculation. In the inoculated area the vascular dilatation was more marked and the diapedesis, although minimal, was somewhat more marked, also. Only a few inflammatory cells were observed however, at any distance from the capillaries and the edematous tissue was remarkably free of cellular infiltration. In many sections large clumps of bacteria were seen embedded in the tissues, without any evidence of cellular activity around them (Plate I, A, B and C). The bacterial counts performed on the exudate fluctuated widely but were all considerably lower than the original counts of the bacterial suspension injected.

The control animals, at room temperature, all showed a well-defined external swelling at the site of inoculation with redness of the skin in a few instances. At autopsy, on gross examination, a small cutaneous abscess was found in all animals. The microscopic picture was characteristic of an acute inflammatory reaction with abscess formation (Plate I—D). The purulent material obtained from the abscess yielded bacterial counts that varied widely, but were definitely higher than those obtained from the animals subjected to cooling. On the basis of subsequent evidence obtained in this research, it is clear that the method employed for obtaining the samples of exudate was defective. The difficulty with which only minute amounts of fluid could be obtained from the edematous cooled tissues repeatedly necessitated resorting to washings, and the clumping observed in the microscopic sections suggested that variable counts could probably be obtained from different parts of the same specimen.

To eliminate these objections the experiments were repeated on other animals. The same procedure was followed but after the completion of the experiment the inoculated tissues were excised widely and the counts made from this whole specimen.

This procedure was first carried out over a period of 24 hours. The number of bacteria recovered from the tissues subjected to cooling was only slightly lower than that injected (Table I). The counts obtained from

TABLE I  
NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES  
AFTER LOCAL COOLING AT 6°C FOR 24 HOURS

No. of Dog	Bacterial Counts Per Cc	
	Suspension	Tissue
43A	$5.9 \times 10^8$	$2 \times 10^8$
45A	$5.9 \times 10^8$	$2 \times 10^7$
11C	$4.9 \times 10^8$	$1 \times 10^8$
6C	$4.9 \times 10^8$	$9 \times 10^8$
20C	$7.8 \times 10^8$	$4.6 \times 10^8$
15C	$7.8 \times 10^8$	$1.8 \times 10^8$

the controls though consistently high, were lower than those obtained from the cooled tissues and lower than the original number injected (Table II)

The bacterial counts obtained after 48 hours of cooling were substantially the same as those observed after 24 hours of cooling (Table III). The controls showed a further reduction in the number of bacteria, the

TABLE II  
NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES  
AFTER 24 HOURS AT ROOM TEMPERATURE

No. of Dog	Bacterial Counts Per Cc	
	Suspension	Tissue
37A	$5.9 \times 10^8$	$6 \times 10^7$
40A	$5.9 \times 10^8$	$1.6 \times 10^7$
9C	$4.9 \times 10^8$	$1 \times 10^7$
2C	$4.9 \times 10^8$	$2 \times 10^6$
22C	$7.8 \times 10^8$	$1.3 \times 10^8$
18C	$7.8 \times 10^8$	$2.4 \times 10^7$

TABLE III  
NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES  
AFTER LOCAL COOLING AT 6°C FOR 48 HOURS

No. of Dog	Bacterial Counts Per Cc	
	Suspension	Tissue
44A	$5.9 \times 10^8$	$1.7 \times 10^8$
41A	$5.9 \times 10^8$	$4 \times 10^7$
8C	$4.9 \times 10^8$	$2.5 \times 10^8$
7C	$4.9 \times 10^8$	$1.5 \times 10^8$
26C	$8.9 \times 10^8$	$2.8 \times 10^8$
23D	$8.9 \times 10^8$	$1.6 \times 10^8$

TABLE IV  
NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES  
AFTER 48 HOURS AT ROOM TEMPERATURE

No. of Dog	Bacterial Counts Per Cc	
	Suspension	Tissue
38A	$5.9 \times 10^8$	$4.5 \times 10^4$
42A	$5.9 \times 10^8$	$8 \times 10^6$
3C	$4.9 \times 10^8$	$8.1 \times 10^7$
1C	$4.9 \times 10^8$	$1.7 \times 10^6$
25D	$8.9 \times 10^8$	$1.5 \times 10^6$
27D	$8.9 \times 10^8$	$2.4 \times 10^6$

counts being lower than those obtained after 24 hours in untreated animals, and markedly lower than the original number of bacteria (Table IV). In both these experiments, the gross appearance of the tissues showed the characteristic changes previously described.

Similar experiments were then carried out with the period of cooling extended to 96 hours. The aspect of the cooled tissues was similar to that found after 48 hours. The amount of subcutaneous edema however, and the vascular congestion were usually greater. In these animals after block excision of the tissues, the number of bacteria recovered approximated roughly the number injected (Table V). In the controls, abscess formation was a constant finding. In many animals, after the required period of time at room temperature, the abscess had ruptured through the skin. A large number of animals had, therefore, to be inoculated before we could obtain six

# COOLING ON INFECTED TISSUES

tissue specimens with an intact skin. The bacterial counts obtained from these tissues were much lower, showing that in this time period the local defense mechanisms had overcome the infecting organisms to a marked degree (Table VI)

TABLE V  
NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES  
AFTER LOCAL COOLING AT 6°C FOR 96 HOURS

No of Dog	Bacterial Counts Per Cc	
	Suspension	Tissue
9E	$8.7 \times 10^8$	$1.8 \times 10^8$
11E	$8.7 \times 10^8$	$1.9 \times 10^8$
12E	$8.7 \times 10^8$	$4.3 \times 10^8$
14E	$6.6 \times 10^8$	$5.4 \times 10^8$
15E	$6.6 \times 10^8$	$6.6 \times 10^8$
16E	$6.6 \times 10^8$	$4.2 \times 10^8$

TABLE VI  
NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES  
AFTER 96 HOURS AT ROOM TEMPERATURE

No of Dog	Bacterial Counts Per Cc	
	Suspension	Tissue
26C	$6.3 \times 10^8$	$1.0 \times 10^3$
48C	$6.3 \times 10^8$	$1.4 \times 10^3$
47C	$6.3 \times 10^8$	$3.4 \times 10^5$
5E	$3.0 \times 10^8$	$8.0 \times 10^3$
6E	$3.0 \times 10^8$	$2.6 \times 10^5$
7E	$3.0 \times 10^8$	$1.0 \times 10^3$

The experimental method was then modified to determine the effects of a return to a normal environment after a preceding period of cooling. Groups of animals were inoculated according to the same technic, and cooling applied to the limb for a period of 48 hours. The animal was then removed from the cooler and left at room temperature for an additional period of 48 to 96 hours. The limbs warmed up very rapidly following removal from the cold bath. Within 48 hours after discontinuing the application of cold, the edema of the limb would disappear, leaving a localized swelling at the site of injection. The results of the examination of this area, in the gross, were very similar to those observed in animals left at room temperature for 48 hours after inoculation. But in most of the animals which had been subjected to a period of cooling the area of inflammatory changes was slightly greater than in the controls. In none, had the abscess broken out through the skin but in some instances, superficial necrotic lesions of the skin were noted. Microscopically, there was a typical acute inflammation that could not be differentiated from that observed in the controls except for the subjective impression that the amount of edema was slightly greater. The bacterial counts obtained from the excised tissues showed a decrease from the original number of bacteria injected and approximated those observed in animals after 48 hours at room temperature without previous cooling (Table VII)

When 96 hours were allowed to elapse after cooling had been discontinued, the individual variations in the gross appearance of the lesion



were greater than in any of the previous experiments. A localized abscess was observed in all cases. While in some instances, the area of inflammation was slightly smaller than that observed after 48 hours, in others it was larger than any observed in the controls after 96 hours. This wide variation was also noted in the bacterial counts obtained from the excised tissues (11 dogs). In some animals the number of bacteria recovered showed only a slight decrease or no change at all, in others, the counts showed a marked decrease over the number of bacteria originally injected (Table VIII).

TABLE VII

NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES AFTER LOCAL COOLING FOR 48 HOURS FOLLOWED BY 48 ADDITIONAL HOURS AT ROOM TEMPERATURE

No. of Dog	Bacterial Counts Per Cc	
	Suspension	Tissue
27C	$6.3 \times 10^8$	$5.8 \times 10^7$
23C	$6.3 \times 10^8$	$1.4 \times 10^5$
29C	$6.3 \times 10^8$	$1.8 \times 10^8$
4D	$5.1 \times 10^8$	$3.9 \times 10^6$
3E	$3.0 \times 10^8$	$4.8 \times 10^4$
4E	$3.0 \times 10^8$	$4.3 \times 10^5$

TABLE VIII

NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES AFTER LOCAL COOLING FOR 48 HOURS FOLLOWED BY 96 ADDITIONAL HOURS AT ROOM TEMPERATURE

No. of Dog		Bacterial Counts Per Cc	
		Suspension	Tissue
1F	....	$8.0 \times 10^8$	$3.4 \times 10^5$
2F		$8.0 \times 10^8$	$1.1 \times 10^5$
3F		$8.0 \times 10^8$	$8.3 \times 10^8$
4F		$8.0 \times 10^8$	$3.7 \times 10^8$
5F		$7.2 \times 10^8$	$3.7 \times 10^4$
7F		$7.2 \times 10^8$	$2.6 \times 10^3$
8F		$7.2 \times 10^8$	$3.9 \times 10^3$
23G		$2.1 \times 10^9$	$4.2 \times 10^6$
24G		$2.1 \times 10^9$	$4.8 \times 10^6$
28G		$2.1 \times 10^9$	$1.6 \times 10^9$
29G		$2.1 \times 10^9$	$1.0 \times 10^9$

Finally, another series of experiments was carried out with the site of inoculation at a greater distance from the surface. In spite of the small bulk of the limb, the wrist joint seemed best suited to this purpose. The joint was inoculated with 0.5 cc of the bacterial suspension. One group of animals was treated by local cooling and the other left at room temperature for periods of 24 and 48 hours.

The control animals did not show, grossly, as severe an acute pyogenic arthritis as had been expected. There was some congestion of the synovia and minute amounts of turbid fluid in the joint. The recovery of "*Streptococcus hemolyticus*" from this fluid, however, established the fact that the joint had been inoculated. Microscopic examination of the capsule showed an acute inflammatory reaction but not of the intensity of that observed in the subcutaneous infections (Plate II, C and D).

In the animals which had been refrigerated the gross appearance of the

limbs was not greatly different. The microscopic sections showed only minimal reactive changes (Fig II, A and B). The bacterial counts obtained from the joint exudate showed the same trend as those reported after subcutaneous injections.

COMMENT—The exposure of inoculated tissues to a temperature of 6° C for periods up to 96 hours results in a definite inhibition of the usual inflammatory response to "*Streptococcus hemolyticus*" encountered in the control animals. This inhibition is evidenced by the gross and microscopic picture

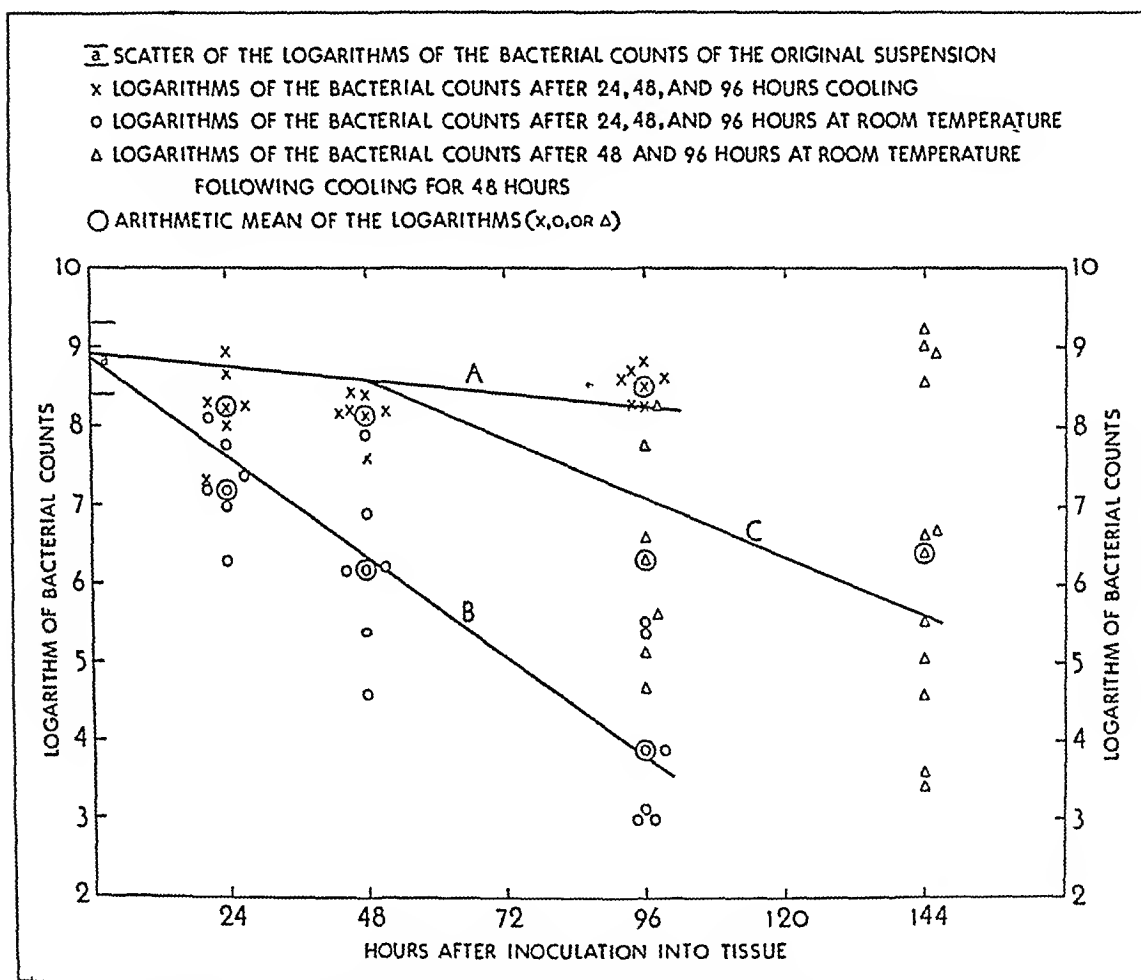


CHART I—A Curve showing that during cooling the number of bacteria in the tissues remains relatively unchanged  
B Curve showing the decrease in the number of bacteria in the tissues which occurs at room temperature  
C Curve indicating the tendency for bacteria to disappear more slowly from the tissues when a period of cooling has preceded the return to a normal environmental temperature

observed after cooling. It is further substantiated by the fact that no significant decrease in the number of organisms injected is observed under these conditions. At room temperature, the decrease in the number of bacteria follows a logarithmic curve. A comparison of these data (Chart I) indicates that cooling delays markedly the rate of destruction of bacteria in living tissue, in spite of the inhibition of growth which probably takes place at low temperatures *in vivo* as well as *in vitro*. In these experiments no attempt was made to determine the proportion of bacteria that had spread to the regional lymph

phatics or that was carried away by the blood stream. Gelatinous edema, vascular congestion and minimal diapedesis were noted throughout the cooled limb, even at a distance from the site of inoculation. The degree of edema seemed related to the length of the cooling period. Finally, these changes were also observed in limbs that were cooled without any previous inoculation. This would suggest that some of the reactive changes observed in the tissues are due to the effects of cold itself. As the limbs were immobilized in a dependent position, dependency could be regarded as an additional factor, although it alone did not produce this lesion. It is noteworthy that this edema, with temporary anesthesia and loss of motor function and the occasional appearance of necrotic skin lesions after the return of the limb to a normal environment, bears a striking resemblance to the clinical syndrome of immersion foot. At the site of inoculation, the pathologic findings were similar but slightly more marked. At the same depth at which these slight reactive changes were found clusters of bacteria without any inflammatory cells around them could be observed. The short, but inevitable, time-lag necessary to reduce the tissue temperature to an adequate level may also be partly responsible for these findings. The evidence seems to indicate that the application of cold in itself for periods up to four days will not have a beneficial effect on the course of a localized infection. At most, a relative *status quo* is present as long as the reduced temperature is maintained. However, the constant finding of diffuse edema in our experiments argues against regarding this condition as a merely innocuous suspension of bacterial and tissue activity.

Brooks and Duncan reported that the area of necrosis which appeared after cooling had been discontinued, was larger than if the lesion developed at body temperature. In their investigation, they were able to study both lesions in the same animal. In our experiments a return, after cooling, to a normal environmental temperature resulted, also, in a grossly more severe inflammation, although the microscopic picture was not significantly different from that observed in the controls. As the lesion under study and the control had to be produced in different animals, individual variations made an exact quantitative comparison difficult. Inasmuch, as the rate of destruction of bacteria after a previous period of cooling will give some measurable indirect evidence of the alteration of tissue response by cold, Chart 1 shows that the trend under these conditions is towards a slower rate of destruction than that observed under normal conditions. The scatter of individual variations in the experiments where cooling had been resorted to widens as the elapsed time increases, and precludes the plotting of an accurate curve. Insofar, as is shown by our data, there is reason to believe that the growth restricting action of the tissues is somewhat decreased by cooling. Statistical studies on a very much larger group of animals may be necessary to substantiate this finding.

The inoculation of joints did not measure up to our expectations as an

experimental procedure Our findings did show, however, that the effects of cooling are manifest even in the deeper structures in spite of their constant perfusion by warm blood In the human, Bierman<sup>4</sup> reported a drop of 10° to 25° F one and one-half inches from the surface of the calf when cold had been applied externally for one or two hours In their experiments Brooks and Duncan noted the appearance of some reactive changes in the subcutaneous tissues while none were observed at the site of the intradermal inoculation They concluded that this is an indication of the relatively small depth of temperature alteration by external applications However, their method of cooling differed greatly from that used in these experiments as they applied cold only to the very limited area of injury This discrepancy between our results and those reported by Brooks and Duncan would seem to lie in the procedure used rather than in the process itself The temporary anesthesia and loss of motor function which follows cooling also provides supportive evidence that the deeper structures as well as the superficial were affected

From these experimental data, it seems evident that the clinical application of cold (6° C) to infected tissue will have no therapeutic value in itself Under certain circumstances, it may not be harmful to cool an infected limb for a brief period in order to maintain the relative *status quo* observed in these experiments in regard to bacterial activity and to tissue response However, under our experimental conditions, cooling for longer periods of time (24 to 96 hours) resulted in definite changes in tissue hydration, in marked vasodilatation and in a decrease in the growth restricting action of tissues towards bacterial organisms Moreover, these changes became more marked as the period of refrigeration was prolonged While the exact clinical limitations of the procedure remain to be determined, this would contraindicate, except for brief periods, the cooling to levels around 6° C of infected limbs which one aims to save by conservative measures

#### SUMMARY

As long as cooling to 6° C is maintained, the subcutaneous tissues of the dog fail to show the inflammatory response usually initiated by the inoculation of "*Streptococcus hemolyticus*" The number of organisms present in the tissues remains remarkably constant and closely approximates the number injected

The development of extensive subcutaneous edema during cooling and after removal of the cold, the development of a more marked inflammatory reaction, with a decrease in the growth restricting power of the tissues to bacterial organisms, suggest the possibility of harmful effects from prolonged refrigeration

The effects of cooling are manifest in the deeper as well as in the superficial tissues of the limb of a dog with an intact blood supply

The clinical implications of the above results are discussed briefly

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# THE EFFECT OF COOLING ON WOUND HEALING<sup>+</sup>

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## GENERAL CONSIDERATIONS

The velocity of many biologic processes varies directly with the temperature. This relationship is expressed in the temperature coefficient ( $Q_{10}$ ) of such processes, which designates the ratio of the rate of the process at one temperature to that at another  $10^{\circ}$  C lower, and frequently follows van't Hoff's law for chemical reactions by falling somewhere between two and three<sup>1</sup>. In some instances, experimental data obtained in studying certain processes, such as velocity of growth, have been found to show changes with temperature with sufficient consistency to permit an expression of the relationship between the two in the form of a mathematic equation<sup>2</sup>. In general, it can be stated that the velocity of most biologic processes is retarded by lowering and speeded-up by elevating the temperature. For example, the rate of division of unicellular organisms (*ameba proteus*) is retarded by lowering the temperature within limits of  $4^{\circ}$  to  $30^{\circ}$  C, and is completely inhibited at  $4^{\circ}$  C,<sup>3</sup> fibroblasts cultured *in vitro* show maximum growth at  $39^{\circ}$  C, the rate diminishing with decrease in temperature, and no growth occurring at or below  $20^{\circ}$  C.<sup>4</sup> More specialized tissues, such as nerve exhibit, a decrease in activity with lowering of the temperature. Conduction time is prolonged, refractory period is lengthened, and the potential associated with conduction is diminished in amplitude.<sup>5</sup> The highly intricate process of metabolism in man is known to vary directly with changes in body temperature, the basal metabolic rate varying some 13 per cent with each degree centigrade change in temperature.<sup>1</sup>

The effect of temperature change on pathologic processes, such as inflammation, has been less thoroughly studied. It is well known that the growth of bacterial organisms is depressed by lowering the temperature, but it is important to remember that in most instances bacteria can be kept alive for long periods at temperatures of  $5^{\circ}$  to  $10^{\circ}$  C without being damaged or destroyed,<sup>6</sup> whereas, prolonged cooling of an extremity of any of the higher animals or man leads to certain harmful effects on the tissues.<sup>7, 8</sup> Brooks and Duncan<sup>9</sup> recently studied intradermal infections in animals following cooling and noticed certain harmful effects both during and after the cooling period. Bruneau and Heinbecker<sup>10</sup> investigated the effects of cooling on subcutaneous and intra-articular infections in dogs. They found that the inflammatory response of the tissues was inhibited during the

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\* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Washington University School of Medicine

period of cooling and exaggerated when normal temperatures were re-established, and that the growth restricting power of tissues to bacterial organisms was inhibited by prolonged cooling. They also noticed that lowering the temperature of a dog's leg for some time produced edema, loss of sensation, and partial or complete paralysis.

The effect of temperature change on the healing of wounds has not been investigated, to our knowledge, although the processes involved in wound healing itself have been studied thoroughly. Among the more important biologic phenomena concerned are ameboid movement, mitotic proliferation, and the maturation of cells. Since these processes have been studied separately, and, in general, have been shown to exhibit velocities varying directly with the temperature, it seems reasonable to assume that wound healing would be adversely affected by lowering the temperature of the part. The present study was undertaken to investigate this problem, with the hope that the results might serve as a basis for determining the indications for the use of refrigeration in clinical surgery. It can be stated that the results observed are such as would have been expected logically to follow from available scientific evidence.

#### EXPERIMENTAL DATA

**Materials and Method** In principle, the experiments performed were quite simple, one of the animal's forelimbs was cooled for a period of from 24 to 72 hours, and the manner in which wounds of the skin and subcutaneous tissue healed was observed, an incision in the opposite uncooled forelimb was used as control. The experiments may be conveniently separated into two series, with three groups comprising the first series, and two, the second.

**Series 1—Group A**—Mongrel dogs weighing from four to eight kilograms were used as experimental animals. The hair was removed from the lateral side of the forelegs, using sodium sulphide as depilator, and the animals were lightly anesthetized with intravenous sodium nembutal. The skin was prepared with iodine and alcohol, and longitudinal incisions, five to six centimeters in length, through the skin and subcutaneous tissue of both lower forelegs, were made with a sharp knife. Hemostasis was secured by pressure, and the skin edges were then approximated without tension by means of interrupted fine silk sutures seven to eight millimeters apart. Thin rubber condoms were next placed over both forelimbs and sutured in place high up on the body, care being taken to see that no constricting effect was present. The animals were then placed in canvas hammocks arranged so that one forelimb was immersed to elbow-level in water maintained by means of a commercial cooling apparatus at a constant temperature of 6° C (with limits of 4° to 8° C) and immobilized there by a tie placed well below the level of the incised area. The other limbs, including the control limb, were immobilized sufficiently to keep the animal within the apparatus, but not completely to prevent movement of the hind limbs. In this way,

the incised forelimb was exposed to cold for a period of 48 hours, without the cold water actually coming into contact with the wound (for exceptions, see later) During this time the animals' food and water intake was unrestricted After the prescribed cooling period the dogs were removed from the apparatus, the condoms were taken off and the animals returned to their cages They subsequently were killed at varying intervals, the wounds studied histologically and estimations of their tensile strength made

The sutures were removed on the seventh day, or before the wounds were studied The tensile strength was measured in grams per centimeter wound length, by a simple clamp or hook and weight-bearing device, an average of two or three determinations being used for each of the computations, cross-sections of the wounds were fixed in formalin, embedded in paraffin, and stained with hemotoxylin and eosin for microscopic examination

Series 1, Group B—These animals were treated in a manner similar to those in Group A, except that the period of cooling was maintained for only 24 hours

Series 1, Group C—These dogs, after having some of the hair of the forelimbs removed with clippers, were placed in the cooling apparatus without condoms over the forelimbs, for 72 hours They were then anesthetized and incisions made in both forelimbs, and immediately sutured The animals then were returned to their cages and wound studies performed at varying intervals as in Groups A and B

Series 2—In the second series of experiments an attempt was made to study the effect of cooling on wounds treated by delayed suture

The forelimbs were prepared as before, incised, and sterile dressings applied Rubber condoms were fixed in place over the forelimbs, and the animals placed in the cooler for 24 or 48 hours On removal from the cooler, the animals were again lightly anesthetized, the dressings removed, the skin around the wound prepared again, and the incisions closed with interrupted fine silk sutures In Group A of this series the cooling period was 24 hours, in Group B, 48 hours The wounds were studied at varying intervals by gross examination, by microscopic section and by estimation of tensile strength as in Series 1

## RESULTS

Series 1, Group A—Gross infection of the wounds occurred in a considerable percentage of cases The results from such animals are not included in the estimations of tensile strength In certain instances the rubber condoms broke, or the animals' struggles allowed water to splash into the container, so that the cold water was in direct contact with the wound Healing in this minority of cases seemed similar to that which occurred in those remaining perfectly dry, and it was, therefore decided that in this particular series it would be permissible to include these results with the others The tensile strengths of all the wounds which healed cleanly are



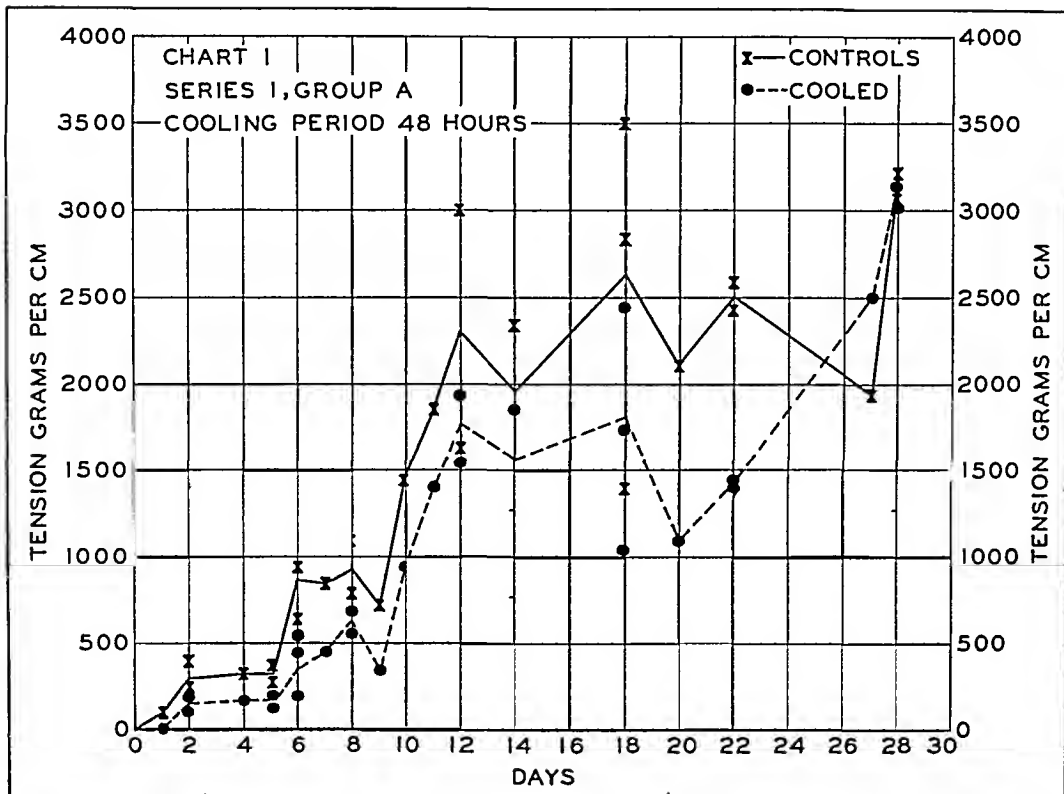


CHART 1—Tensile strength measurements of wounds during the healing period "X" marks the average tensile strength of one control wound in Gm/cm, and "O" the average strength of a cooled wound. Where more than one animal was killed at any particular time during the healing process, the curve is drawn through the averaged value of the individual determinations.

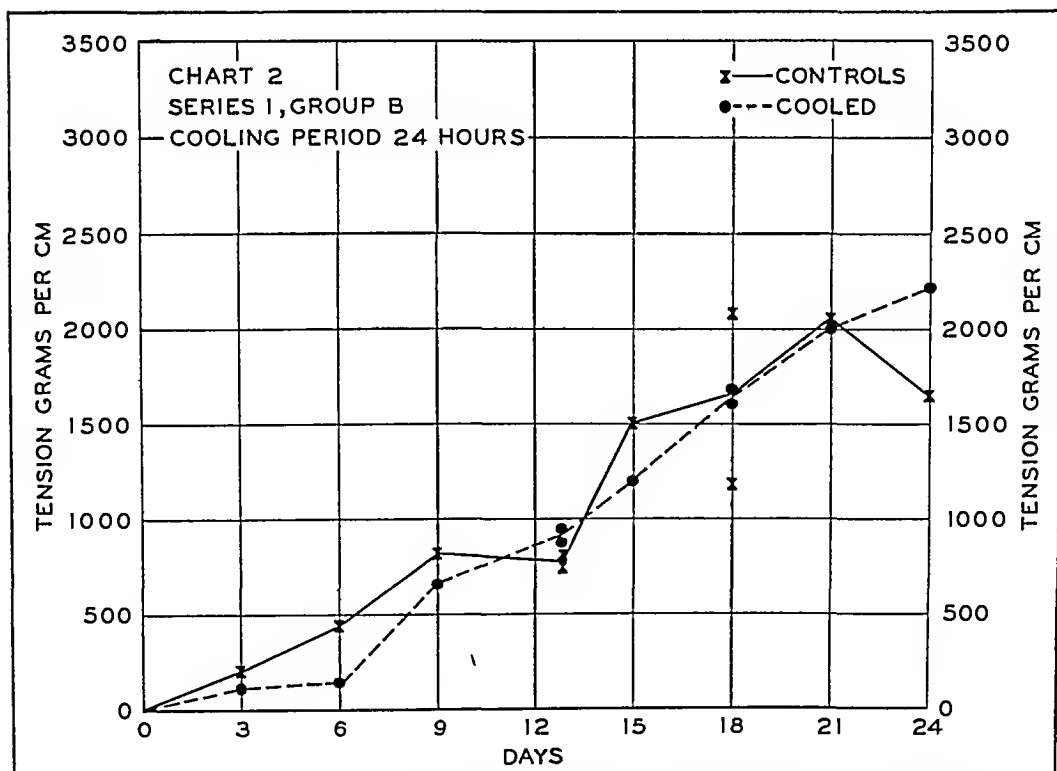


CHART 2—Tensile strength measurements of wounds during the healing period "X" marks the average tensile strength of one control wound in Gm/cm, and "O" the average strength of a cooled wound. Where more than one animal was killed at any particular time during the healing process, the curve is drawn through the averaged value of the individual determinations.

given in Chart 1. A total of 55 dogs was studied in this group, but 28 of them had to be discarded because of disease or infection. The chart, thus, depicts the relative strength of 54 wounds in 27 dogs during various phases of the healing period.

These results may be compared with Charts 2 and 3, which give the results of those experiments in which cooling was performed for 24 and 72 hours, Groups B and C of this series, respectively. Although these latter experiments were done on smaller numbers of animals, the results are sufficiently uniform to be useful for purposes of comparison.

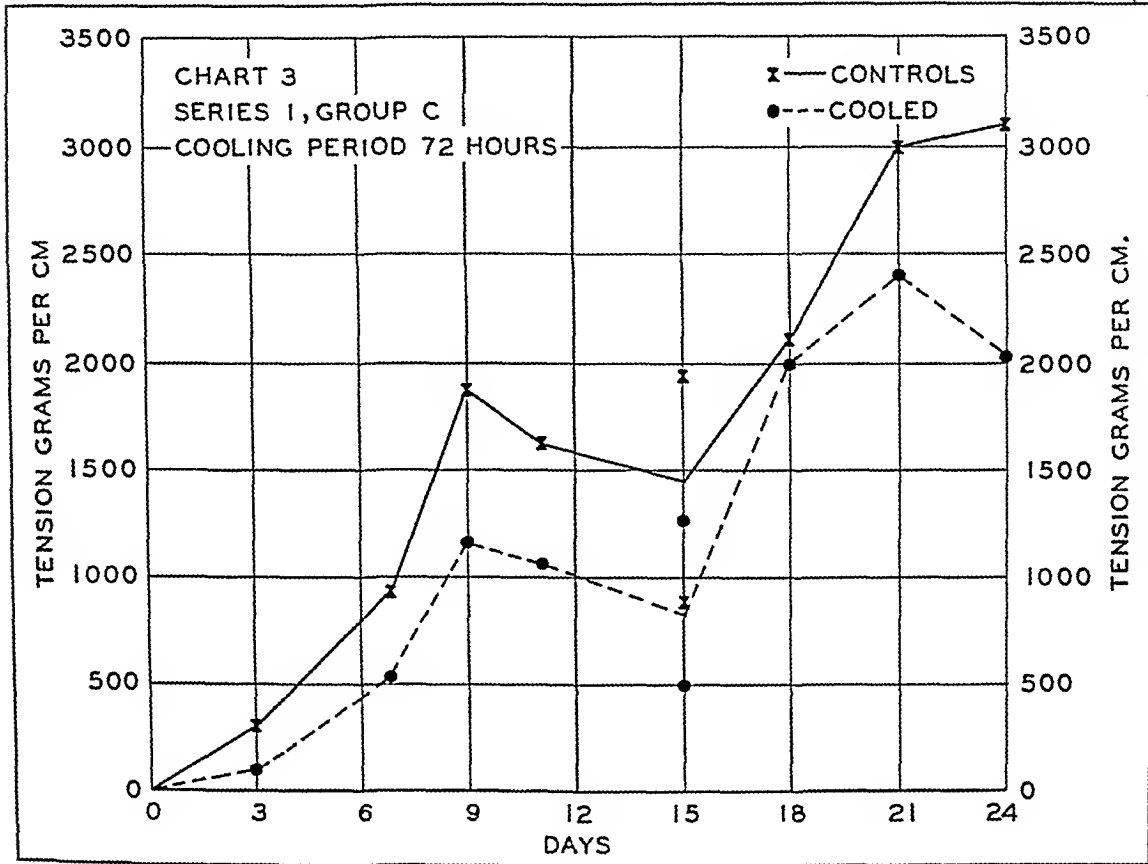


CHART 3—Tensile strength measurements of wounds during the healing period. "X" marks the average tensile strength of one control wound in Gm/cm., and "O" the average strength of a cooled wound. Where more than one animal was killed at any particular time during the healing process, the curve is drawn through the averaged value of the individual determinations.

The histologic appearance of the healing wounds in these experiments varied considerably (Fig 1-4). The incidence of infection in the 72-hour group was high, four of a group of nine dogs showed definite evidence of infection of the refrigerated wounds, while only one of the controls became infected. In all three groups the wounds not infrequently displayed some microscopic widening or infiltration with inflammatory cells, even though no gross evidence of infection was present. Otherwise, the healing process, as evidenced by histologic findings, seemed to parallel the charted estimations of tensile strength. It is noteworthy that sections of the incisions taken immediately after cooling showed no microscopic evidence of tissue

response to the injury, whereas beginning healing was evident in the controls (Fig 1)

Series 2—The results obtained in the second series of experiments, where the limb was incised, then cooled, and sutured after the cooling period, were difficult to assess from the point of view of clean healing. Only those results were included in which the wounds remained dry, without leakage or tearing of the protective rubber envelope. In Group A

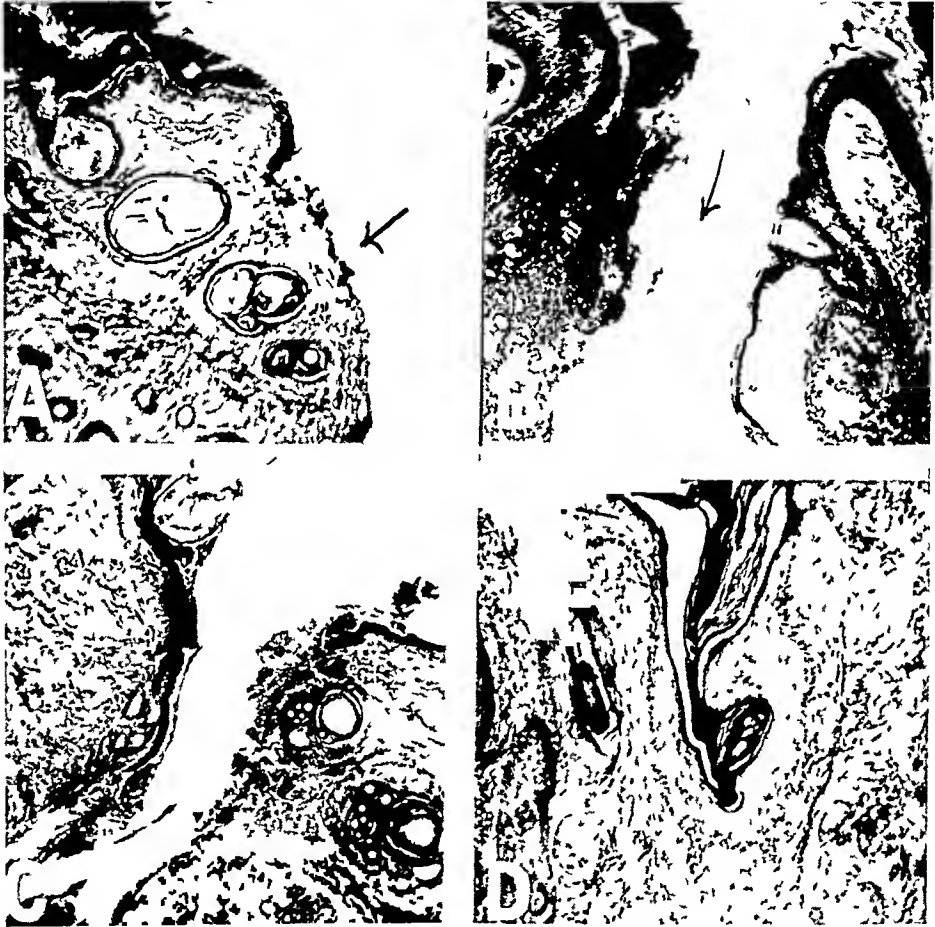


FIG 1—Photomicrographs ( $\times 60$ ) of tissues stained with hematoxylin and eosin, from Series 1, Group A, in which the cooling period was 48 hours

A and B Sections of wounds immediately following the cooling. An arrow designates the wound edge in each. Note absence of reaction in cooled wound A, with exudate of inflammatory cells and fibrin in control B

C and D From dogs three days after the cooling period. Note slight cellular reaction in the cooled wound C, epithelization with beginning fibroplasia in control D

(cooling period 24 hours) six of the nine dogs used developed gross infection of the wound in the cooled limb, while only two of the controls became infected. However, the infected wounds healed rapidly, once the pus had been discharged, both in the cooled and control limbs. Tensile strength in such wounds, as modified by the frequent presence of infection, are given in Chart 4. Histologic studies confirmed the evidence of gross infection in each case (Fig 5). In the second group of this series, Group B (cooling period 48 hours) the results were similar but more marked. Of

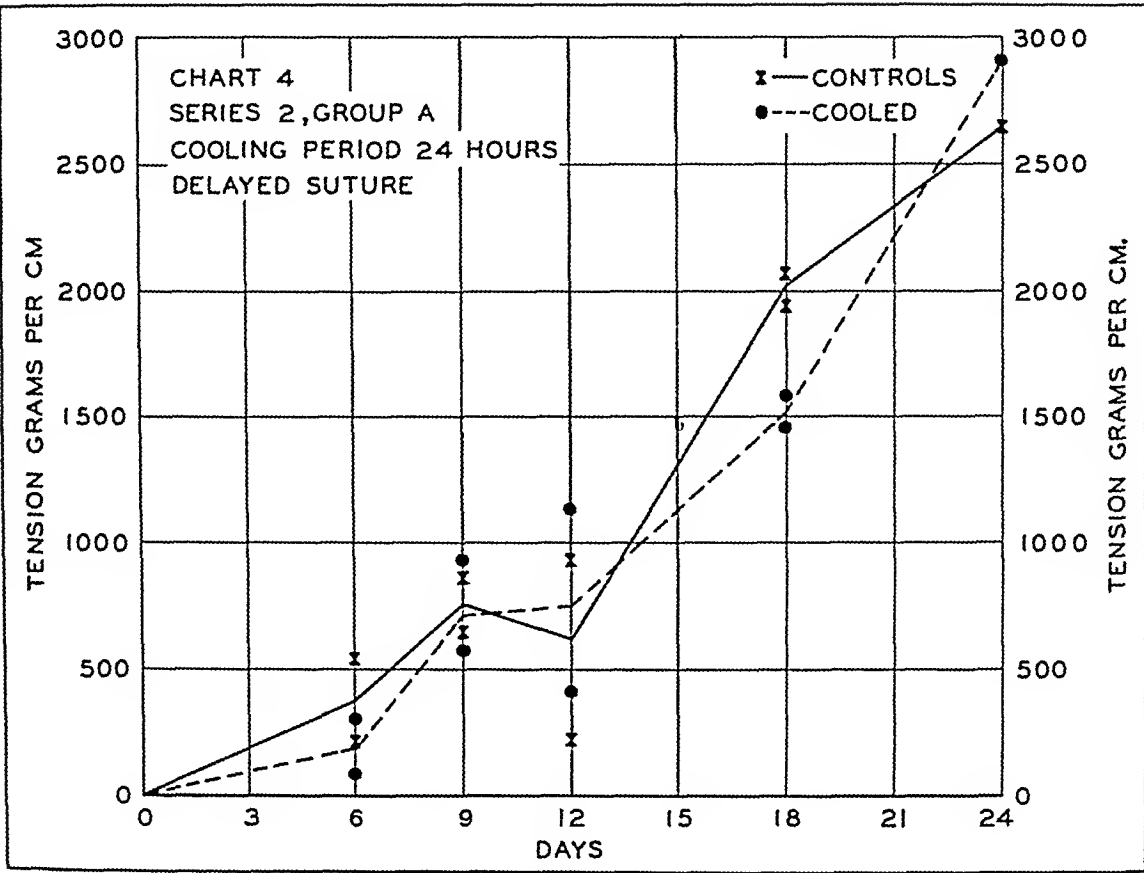


CHART 4—Tensile strength measurements of wounds during the healing period "X" marks the average tensile strength of one control wound in Gm/cm, and "O" the average strength of a cooled wound. Where more than one animal was killed at any particular time during the healing process, the curve is drawn through the averaged value of the individual determinations.

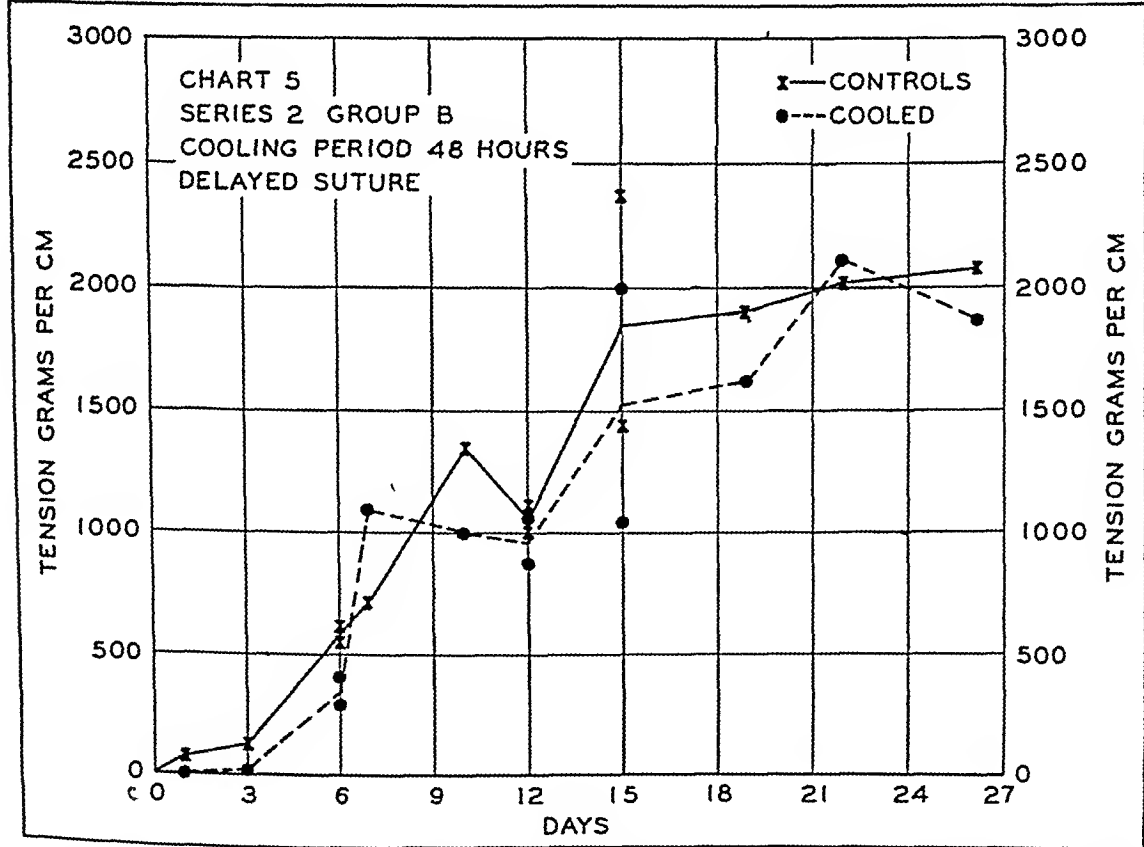


CHART 5—Tensile strength measurements of wounds during the healing period "X" marks the average tensile strength of one control wound in Gm/cm, and "O" the average strength of a cooled wound. Where more than one animal was killed at any particular time during the healing process, the curve is drawn through the averaged value of the individual determinations.

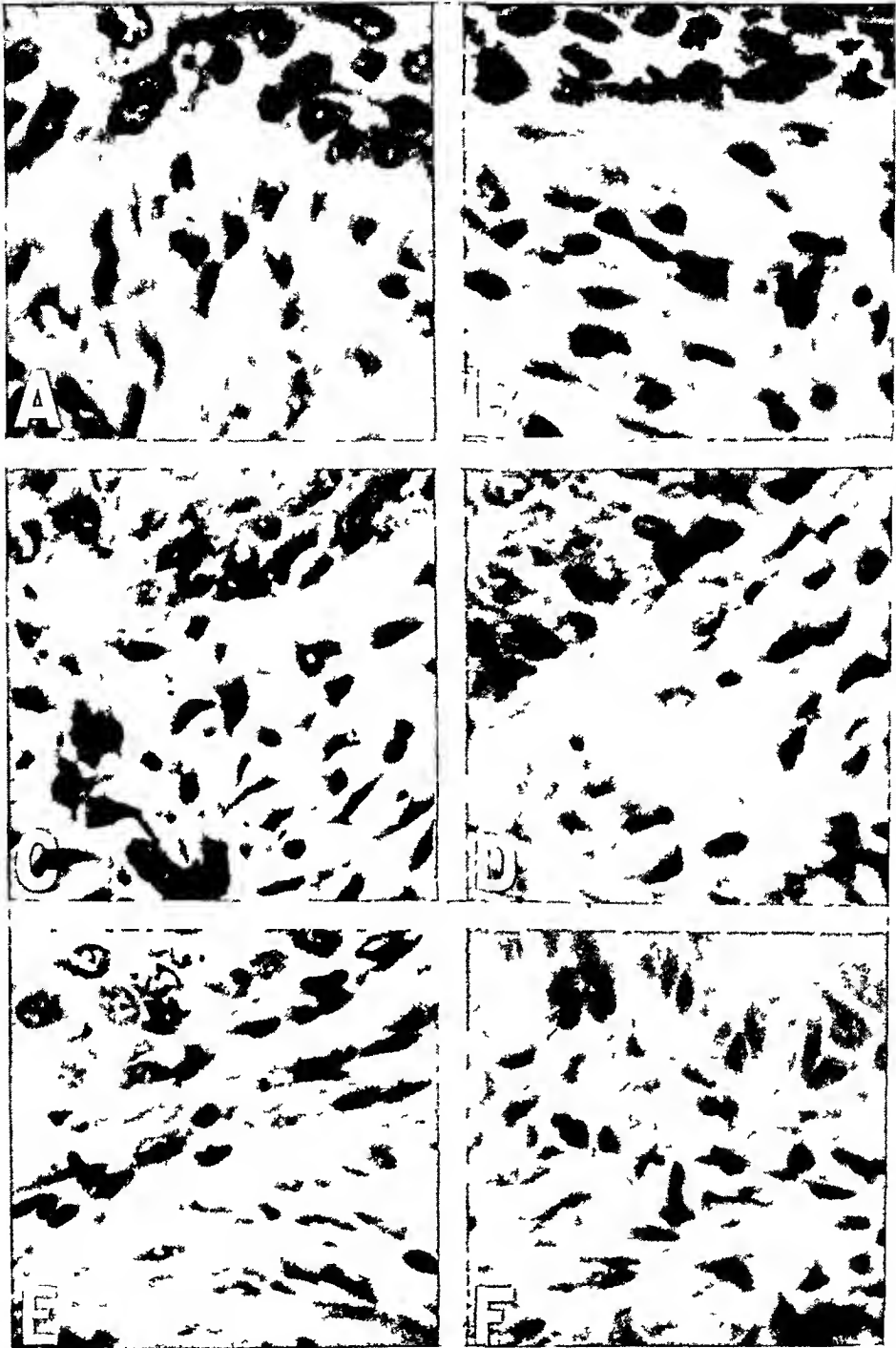


FIG 2—Photomicrographs ( $\times 575$ ) of tissues from Series 1, Group A, in which the cooling period was 48 hours

Sections marked A, C and E from cooled wounds, those marked B, D and F from corresponding controls. A and B, 6 days, C and D, 8 days, E and F, 12 days following the cooling period. Note slightly greater edema, less regularity of fibroblasts and poorer deposition of collagen in the cooled wounds

13 dogs used, nine of the incisions in the cooled limbs and only one of the control wounds became infected. The tensile strengths of these wounds are given in Chart 5. Histologic confirmation of infection, again, found in every case, is shown in the photomicrographs of Figure 6.

Another significant feature was noticed in this latter series of experiments. When the animals were removed from the cooler and the dressings taken off, the uncooled control incision showed pinkish, firm beginning granulations, whereas, the cooled limb appeared as it had when incised 24 or 48 hours previously.

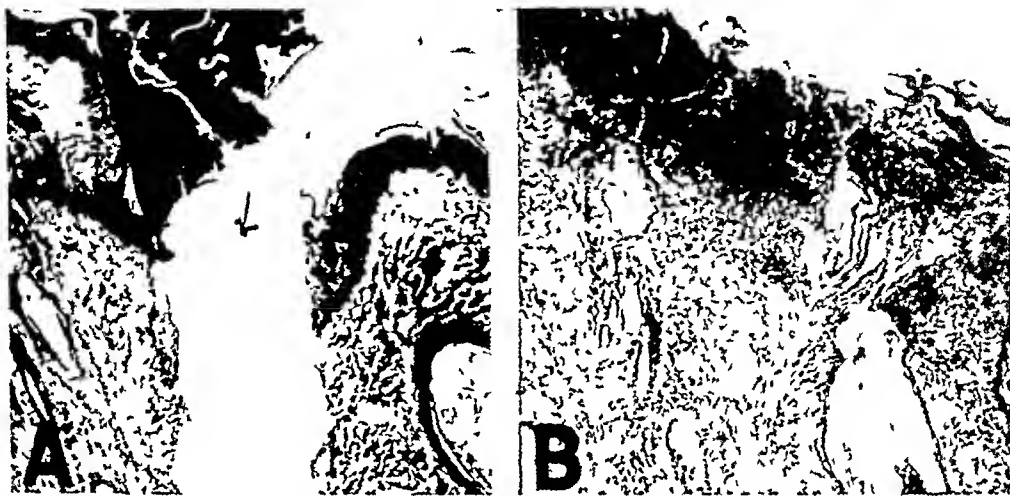


FIG. 3—Photomicrographs (X60) of tissues from Series 1, Group C, in which the cooling period was 72 hours.  
A and B Sections taken three days after cooling. Note absence of reaction and hemorrhage on the surface of the cooled wound A. An arrow indicates the wound area.

**DISCUSSION**—The results of the first series of experiments permit a comparison of the healing process in cooled with that in uncooled limbs. They show (1), that during the cooling period there is no response to the trauma of the incision, (2), that for any given period during the healing process the cooled incisions exhibit a delay in healing, as evidenced by measurements of tensile strength, (3), that when cooling is prolonged (48 to 72 hours) the lag in healing is most marked late in the course of the healing process, and (4), that the degree of delay in healing is roughly proportional to the duration of the cooling period (Chart 6). It is significant that cooling a limb for two days results in sufficient damage to the tissues to cause a marked effect on wound healing for more than two weeks after the actual cooling period.

The results of the second series of experiments show that prolonged refrigeration of a wound followed by delayed suture results in a higher incidence of infection than would have been the case if cooling had not been used. The high incidence of infection in those wounds made and sutured after cooling the limb for 72 hours (Series 1, Group C) indicates that very prolonged refrigeration results in greater risk of infection, even if the wounds are sutured immediately. It is interesting that this increased incidence of infection in cooled incisions gives direct confirmation to the

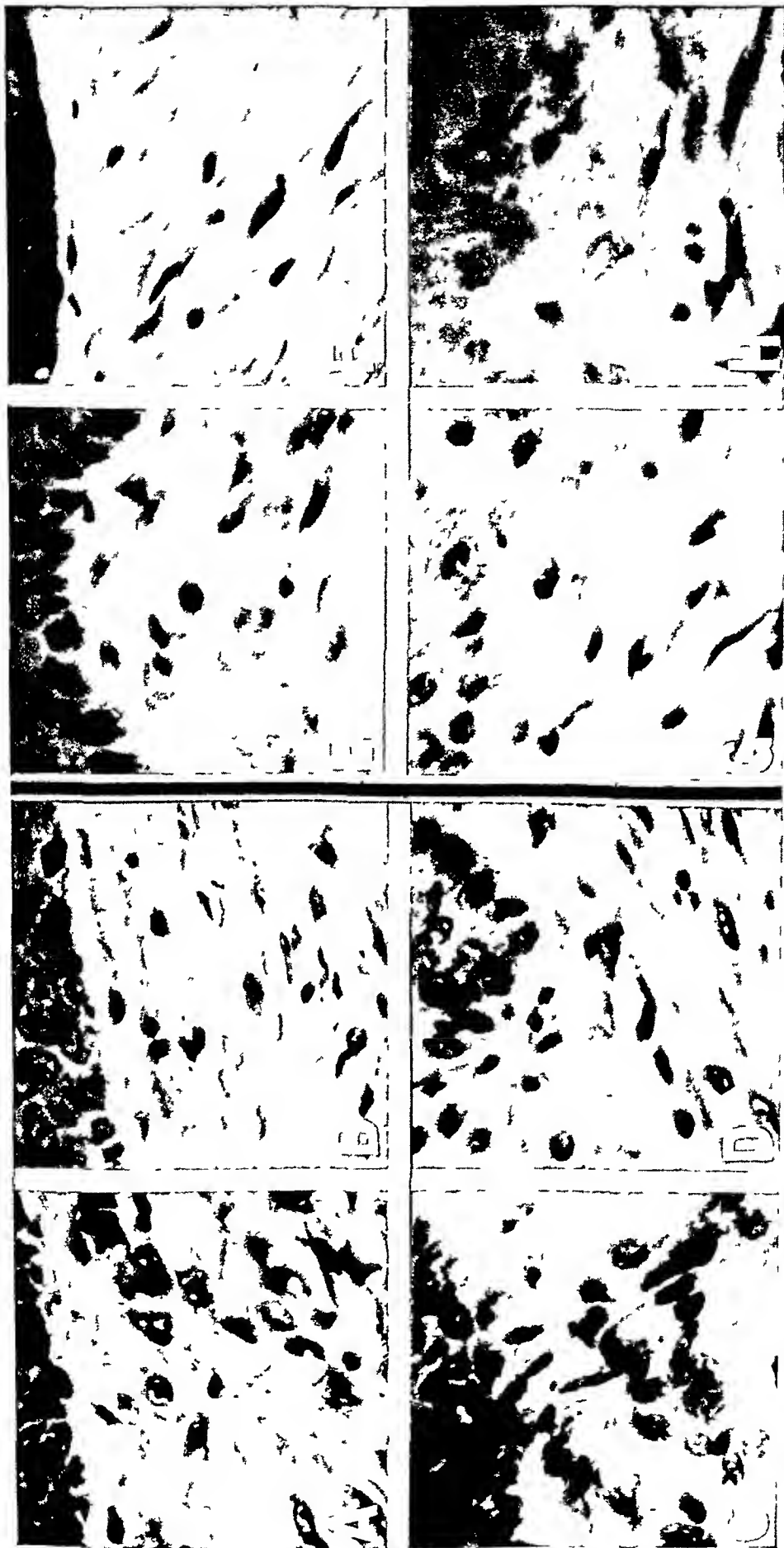


FIG. 4—Photomicrographs ( $\times 575$ ) of tissues from Series 1, Group C, in which the cooling period was 72 hours.  
A, C, E and G from cooled wounds, B, D, F and H from corresponding controls. A and B, 9 days, and D, 11 days, E and F, 15 days, G and H, 21 days following cooling. Note that the wounds in cooled tissues show irregular growth and immaturity of the fibroblasts. The amount of collagen formed is less. Note that the degree of retardation of wound healing is more marked than in comparable wound cooled for 48 hours (Fig. 2).

## COOLING ON WOUND HEALING

work of Brooks and Duncan<sup>9</sup> and of Bruneau and Heinbecker,<sup>10</sup> who found, as already mentioned, that prolonged refrigeration of contaminated or infected tissue results in certain harmful after effects.

The mechanisms involved in the production of the harmful effects on wound healing following refrigeration merit further comment. For although inhibition of the healing process would be expected to occur during the cooling period, in accordance with the known retardation of biologic processes at lower temperatures, the extent of the damage was actually found

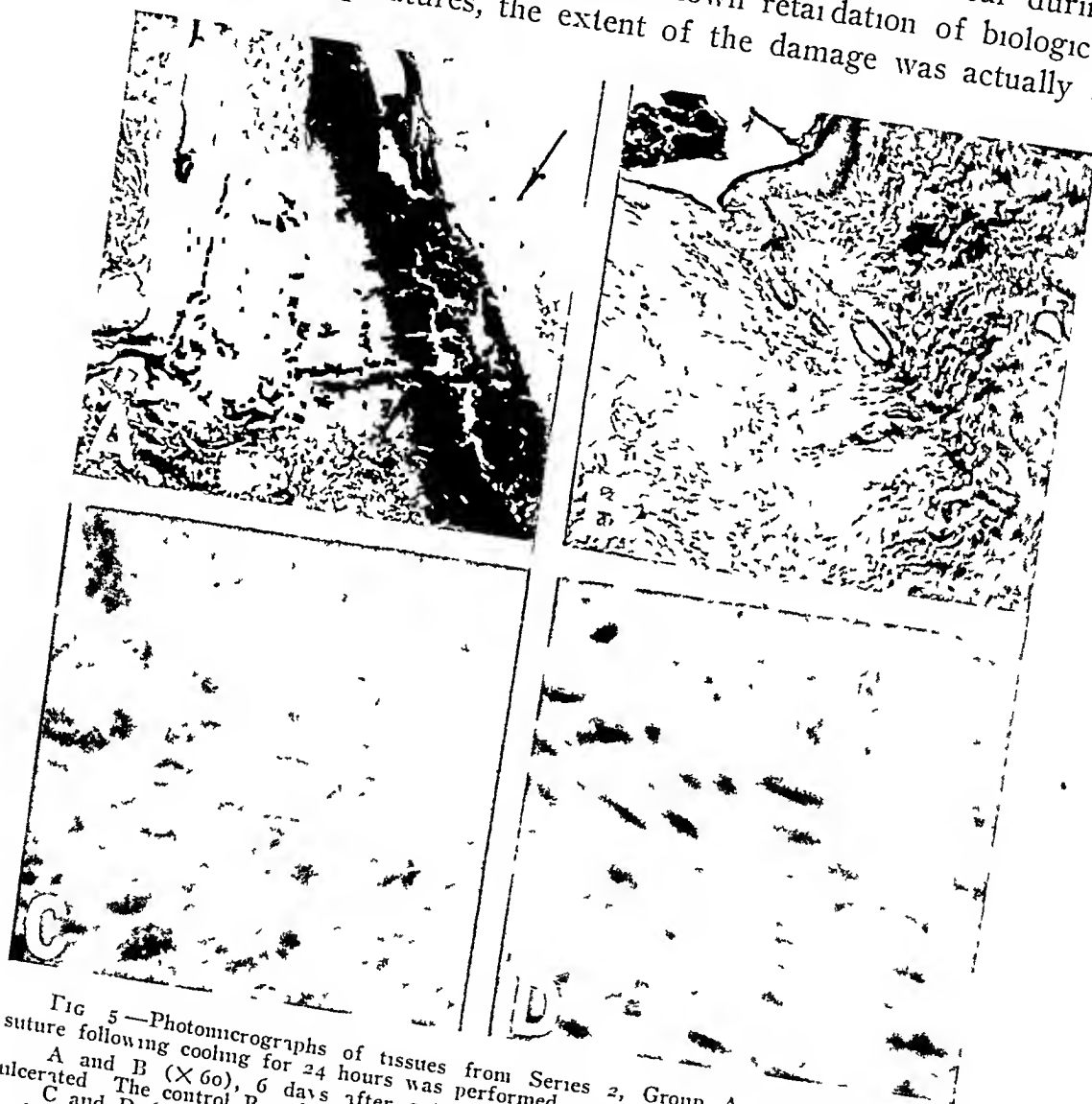


FIG 5—Photomicrographs of tissues from Series 2, Group A, in which delayed suture following cooling for 24 hours was performed. The cooled wound A is wide open and A and B ( $\times 60$ ), 6 days after suture. The control B is healing with considerable fibroplasia. The fibroblasts are large and less mature. C and D ( $\times 575$ ), 12 days after suture. The cooled wound C shows more inflammatory cells in the wound space and in the tissues than in the control D.

to be much greater after the cooling agent had been removed. An explanation of these findings is revealed by an analysis of the local factors known to influence wound healing. These include, (1), the amount of killed or damaged tissue in the wound surfaces, (2), the integrity of the blood flow to the damaged tissues, this determines the nutrition and viability of the tissues bordering on the wound surfaces, (3), the amount and character of the exudate in the wound space and in the tissues



bordering the wound, (4), the number and character of pathogenic organisms in the wound space and bordering tissues, and (5), the number and character of foreign bodies to be extruded or encapsulated<sup>11</sup> In our experiments the amount of damaged tissue and the number of pathogenic organisms and foreign bodies (sutures) were constant for control and cooled limbs There remain for consideration the integrity of the blood

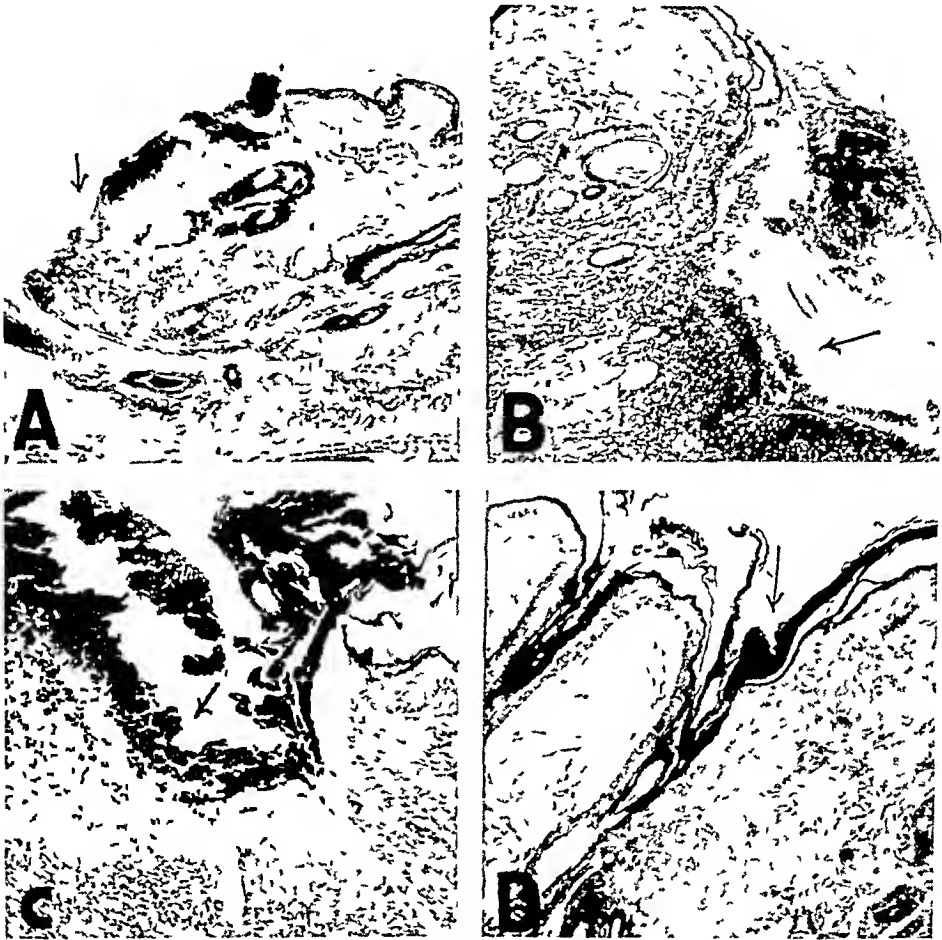


FIG 6—Photomicrographs ( $\times 60$ ) of tissues from Series 2, Group B, in which delayed suture following cooling for 48 hours was performed An arrow designates the wound in each section

A and B, directly after cooling, there is no reaction in the cooled wound A, marked exudation in the control B

C and D, 6 days after cooling and suture The cooled wound C is wide open and ulcerated, the control D is healing cleanly

flow to the part and the amount and character of the exudate formed Lowering the temperature of the involved tissues changes both of these latter factors in a manner tending to delay wound healing and to promote bacterial growth For it is known that prolonged cooling of an extremity results in decreased blood flow through the part and in the production of interstitial edema<sup>8</sup> The deficiency of blood supply and the edema often remain long after the temperature has been restored to normal, and this accounts for the prolonged derangement of wound healing A further contributing factor may be trophic changes associated with degeneration of the

peripheral nerves, which has been shown to occur after prolonged exposure of an extremity to cold<sup>12</sup>

#### CLINICAL IMPLICATIONS

The results of our experiments, together with those of Bruneau and Heinbecker, indicate that certain harmful effects result from prolonged refrigeration of living tissue, such as is advocated by some for amputation of gangrenous infected extremities. It may be held that, because the duration of the cooling period as applied clinically is often much shorter than that

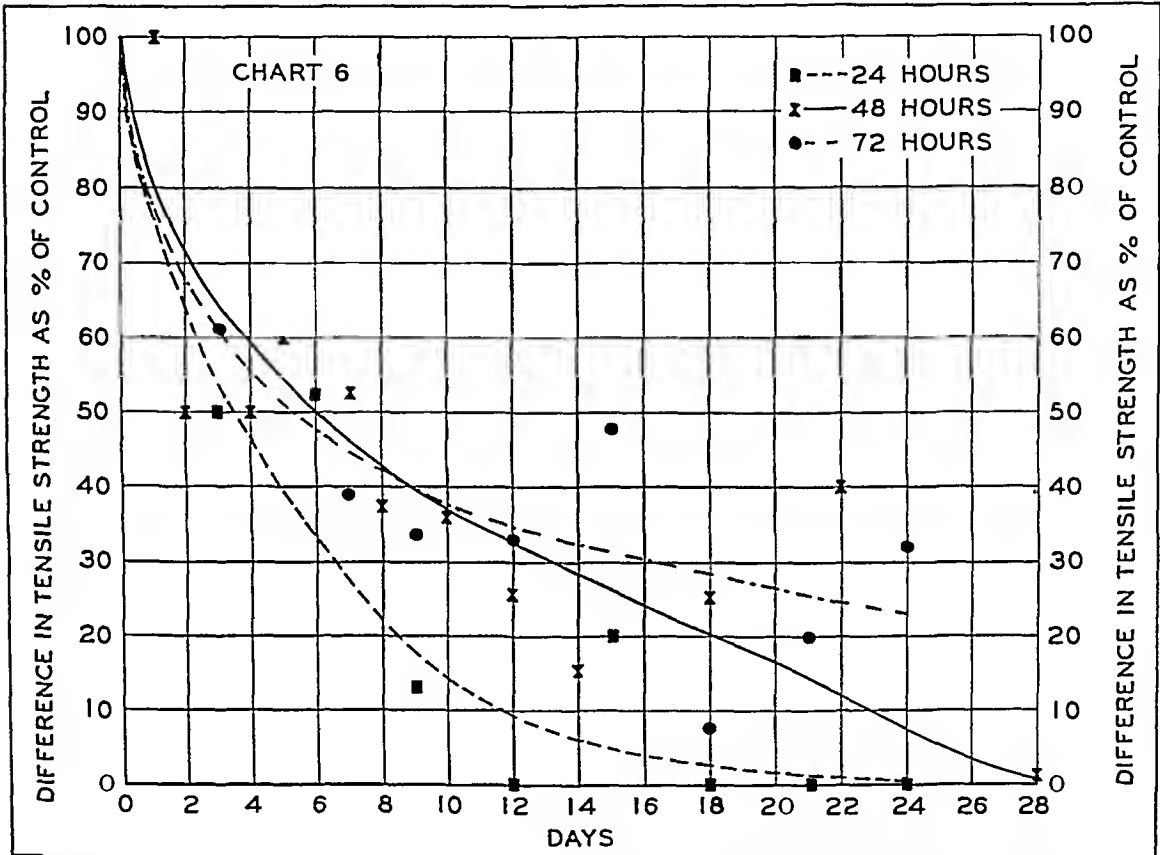


CHART 6—The difference in tensile strength measurements between cooled and control wounds, plotted as percentages of the controls. They indicate the degree of delay in healing for any given period during the healing process. The data are obtained from Charts 1, 2 and 3, and are plotted as scatter diagrams, the curves occupying mean positions.

Since healing does not occur during the cooling period, the discrepancy between cooled and control is 100 per cent immediately after cooling. It gradually approaches zero over a period of three or four weeks. Note that the 72 hour curve overlaps the 48 hour curve early in the period of healing, a consequence of the fact that the incisions for the 72 hour group were made *after* the cooling period, while those of the 48 hour group were made *before* cooling. In effect, then, the incisions in the 48 hour controls had a two days' start in healing.

employed in these experiments, the results are not comparable. Since it has been shown that the harmful effects are proportional to the duration of the cooling period, it may be assumed that some degree of harm must result whenever living tissues are cooled to low temperatures. It is felt, therefore, that refrigeration anesthesia is not ideal for amputations. If the aim is to diminish absorption from a gangrenous region by local cooling, this can be accomplished by refrigerating the limb below the desired amputation level in order that the anesthesia so induced will permit the appli-

cation of a tight tourniquet After restorative measures have been effective, amputation then can be carried out under ordinary anesthesia above the level of cooling without harmful sequelae

Suggestions have been advanced recently by Crossman, Allen, *et al*,<sup>13</sup> McElvenny,<sup>14</sup> and others, that wounds of the extremities incurred on the battlefield be refrigerated during transportation and until proper emergency surgical treatment can be instituted, an interval of many hours or even days Our experiments dealing with the effect of prolonged cooling on wounds treated by delayed or secondary suture fairly closely approximate such war conditions Because of the increased incidence of wound infection after the cooling period shown to occur in these experiments, it is recommended that wounds sustained on the battlefield should not be treated by refrigeration unless there is no hope of saving the part

#### SUMMARY

Experiments were carried out on dogs to study the effects of prolonged refrigeration on wound healing The nature of the healing process in clean incised wounds of the skin and subcutaneous tissues of the forelimb after cooling to 6° C for a period of 24 to 72 hours was determined, using similar incisions in the opposite limb as controls The healing process was studied by measurements of the tensile strength and by microscopic examination of the wounds at varying intervals The results show that during the cooling period there is no reaction on the part of the tissues to the injury inflicted by the incision, and that subsequently there is a definite lag in the healing of the wounds, the degree of delay varying with the duration of the cooling period In wounds treated by delayed suture after cooling for 24 or 48 hours the incidence of infection is much greater than in control incisions maintained at normal temperatures

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# NERVE DEGENERATION FOLLOWING PROLONGED COOLING OF AN EXTREMITY\*

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IN THE COURSE OF RECENT STUDIES on the effect of refrigeration on infection<sup>1</sup> and on wound healing,<sup>2</sup> it was noticed that many of the animals used in the experiments exhibited findings in their extremities similar to those of "immersion foot." The purpose of this communication is to report certain changes found in the peripheral nerves following prolonged cooling.

## METHOD

Small mongrel dogs weighing four to eight kilograms were used as experimental animals, 20 of them were used in the experiment. The hair of the forelimbs was partly removed with clippers and the animals were suspended in canvas hammocks so that one forelimb was immersed to approximately elbow level in cold water thermostatically maintained at a temperature of 6° C. The limbs were immobilized by tape ties over gauze wrapped around the wrists and ankles, and the animals were kept in the apparatus for 96 hours, during which time their food and fluid intake was not restricted. They then were returned to their cages and were sacrificed after varying intervals, up to three months following exposure, but before death the threshold to faradic stimulation of the ulnar nerves in the forelimbs was determined. After sacrifice, the superficial anterior and deep ulnar nerves from the cooled limbs were stained with osmic acid, and impregnated with silver according to the technic of Davenport.<sup>3</sup> Sections of the other tissues, including skin, subcutaneous tissues, vessels and muscles were fixed in formalin, embedded in paraffin, sectioned at 5 microns, and stained with hematoxylin and eosin. Corresponding sections from the tissues of the opposite uncooled forelimbs served as controls.

## RESULTS

Swelling of the involved limb and partial or complete loss of sensation and paralysis usually were present on removal from the cooler, these signs gradually subsiding over a period of several days. The signs were less marked in well nourished animals, evidently because they moved about more while in the apparatus. The threshold for muscle response to faradic stimulation of the ulnar nerve of the involved limb increased until the fifth day after cooling, when, in most instances a response no longer was obtained on maximal stimulation. The threshold then decreased gradually until about

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\*The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Washington University School of Medicine.

# NERVE DEGENERATION FROM COOLING

the 16th day after cooling, when it was again normal, remaining so thereafter

Slight histologic changes only were demonstrable in the skin, subcutaneous tissues and muscles. A measure of edema involved all the tissues, including the intermuscular planes, and the walls of the smaller blood vessels, but there were no infiltrations of inflammatory cells. After the edema had subsided, no

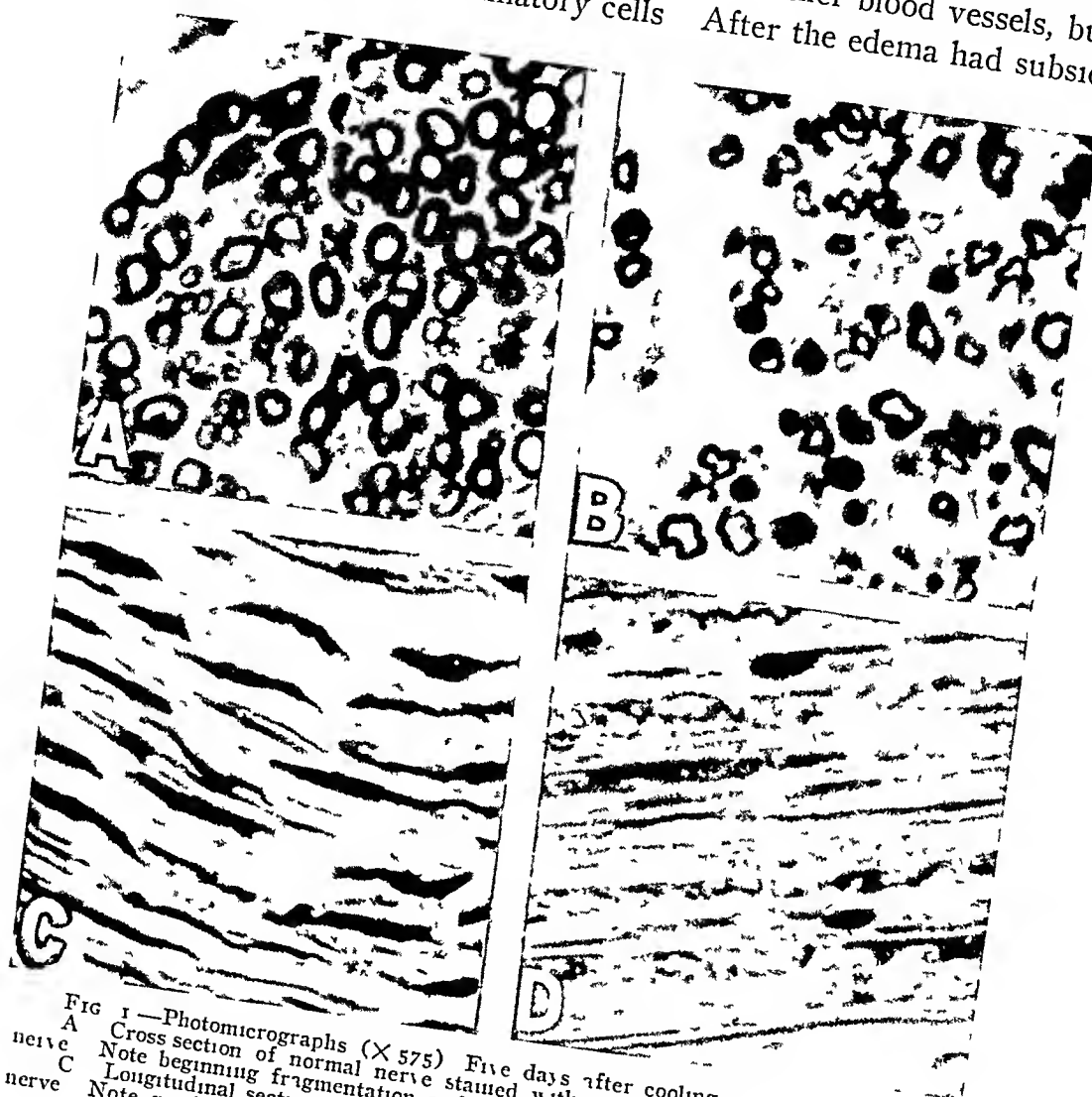


FIG 1—Photomicrographs (X 575) Five days after cooling  
A Cross section of normal nerve stained with osmic acid B Same of cooled nerve  
C Note beginning fragmentation and disappearance of myelin D Same of cooled nerve  
C Longitudinal section of normal nerve stained with silver D Same of cooled nerve  
Note marked swelling, fragmentation, and vacuolization of axon cylinders

difference between cooled and control limbs could be detected microscopically, except for questionable slight fibrosis of the derma and of the subcutaneous tissues

Contrasted with these minimal findings were the marked degenerative changes noted in the nerves of the cooled area. Swelling of the nerve trunks accompanied the generalized edema of the limb and persisted longer, the cooled nerve trunk often being twice the diameter of the control for ten days, or more, after exposure. Both superficial and deep nerves were involved, the former possibly slightly more than the latter. The microscopic sections revealed varying degrees of wallerian degeneration, as evidenced by frag-

mentation and disappearance of the myelin sheaths, and in certain instances, by swelling, vacuolization and fragmentation of the axis cylinders. These histologic changes were evident five days after cooling, and progressed slowly thereafter, some degree of nerve damage being demonstrable for the entire duration of the experiment (*i e*, up to three months after exposure). In most of the nerves studied, the degeneration was patchy in character, but seemed to involve large myelinated, small myelinated, and nonmyelinated

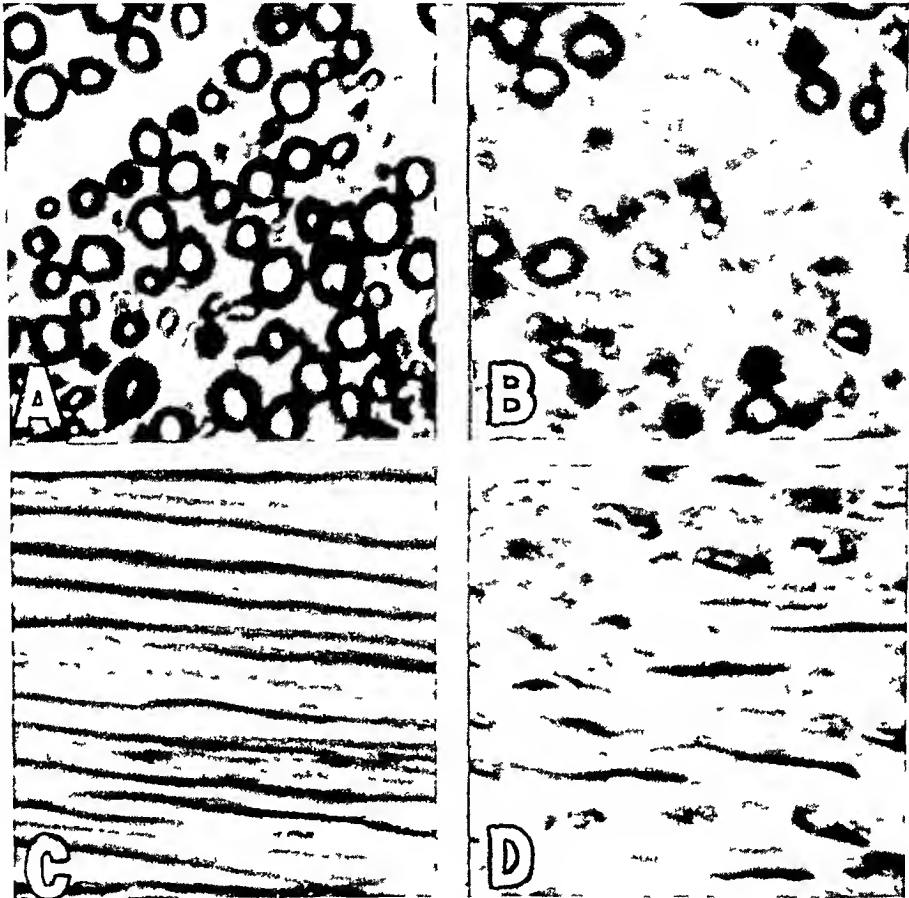


FIG 2—Photomicrographs ( $\times 525$ ) Nine days after cooling  
 A Cross section of normal nerve stained with osmic acid B Same of cooled nerve Note progression of demyelination  
 C Longitudinal section of control nerve stained with silver D Same of cooled nerve Note fragmentation of axones

fibers to an almost equal degree. Illustrative sections are shown in the accompanying figures. As would be expected, the extent of nerve damage was found to vary directly with the amount of edema and paralysis of the limb following cooling, but organic changes of some degree were present in the nerves invariably even in those instances where no gross evidence of edema or paralysis had been discernible at any time.

**DISCUSSION**—The mechanism of production of the changes observed following cooling of an extremity is of interest. The finding of degeneration of the nerves without concomitant inflammatory changes in the other tissues favor the commonly held view that relative ischemia of the part, rather than

# NERVE DEGENERATION FROM COOLING

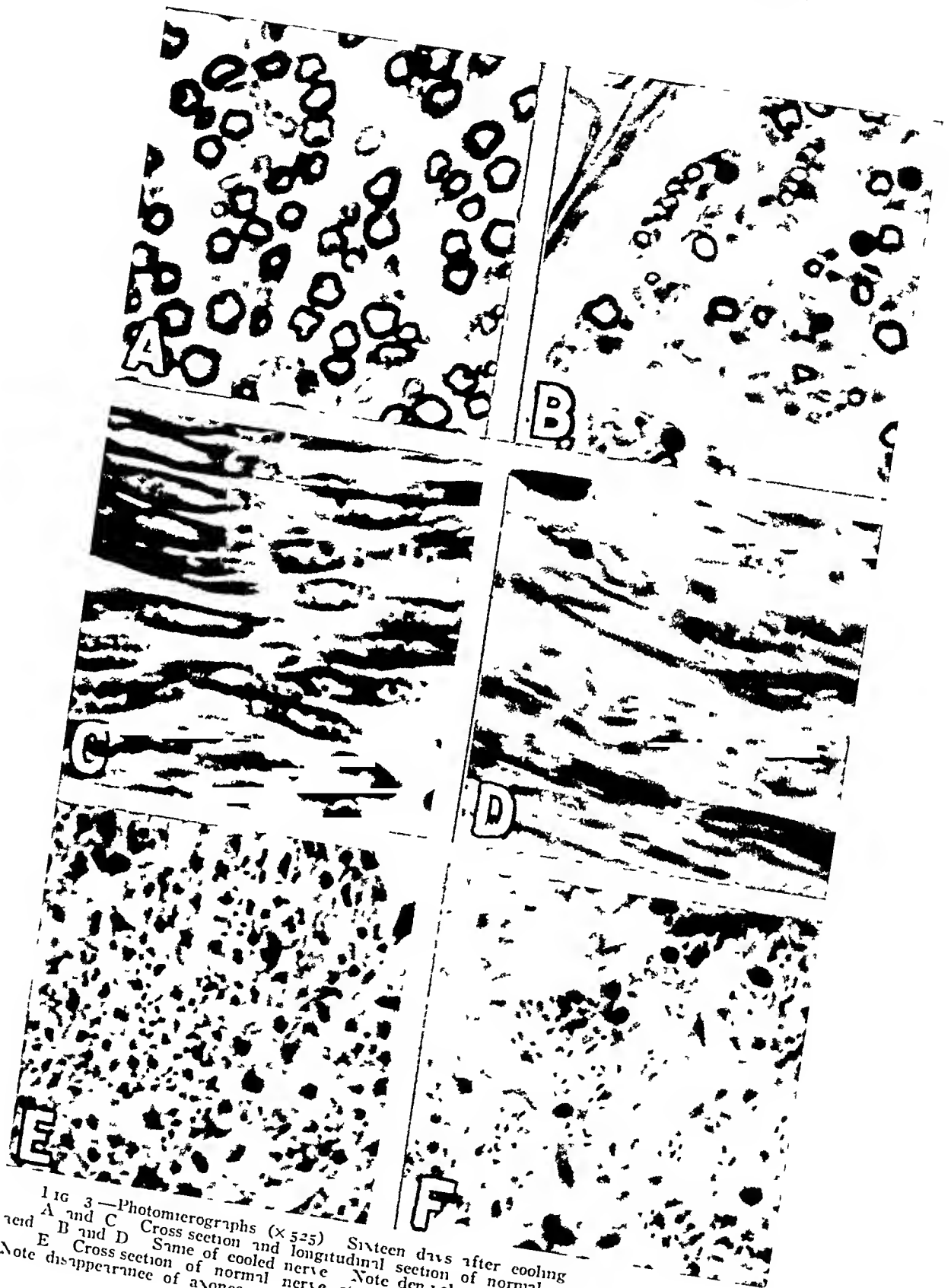


FIG. 3—Photomicrographs ( $\times 525$ ) Sixteen days after cooling  
A and C Cross section and longitudinal section of normal nerve stained with osmic acid  
B and D Same of cooled nerve Note denervation  
E Cross section of normal nerve stained with silver  
F Same of cooled nerve Note disappearance of axons



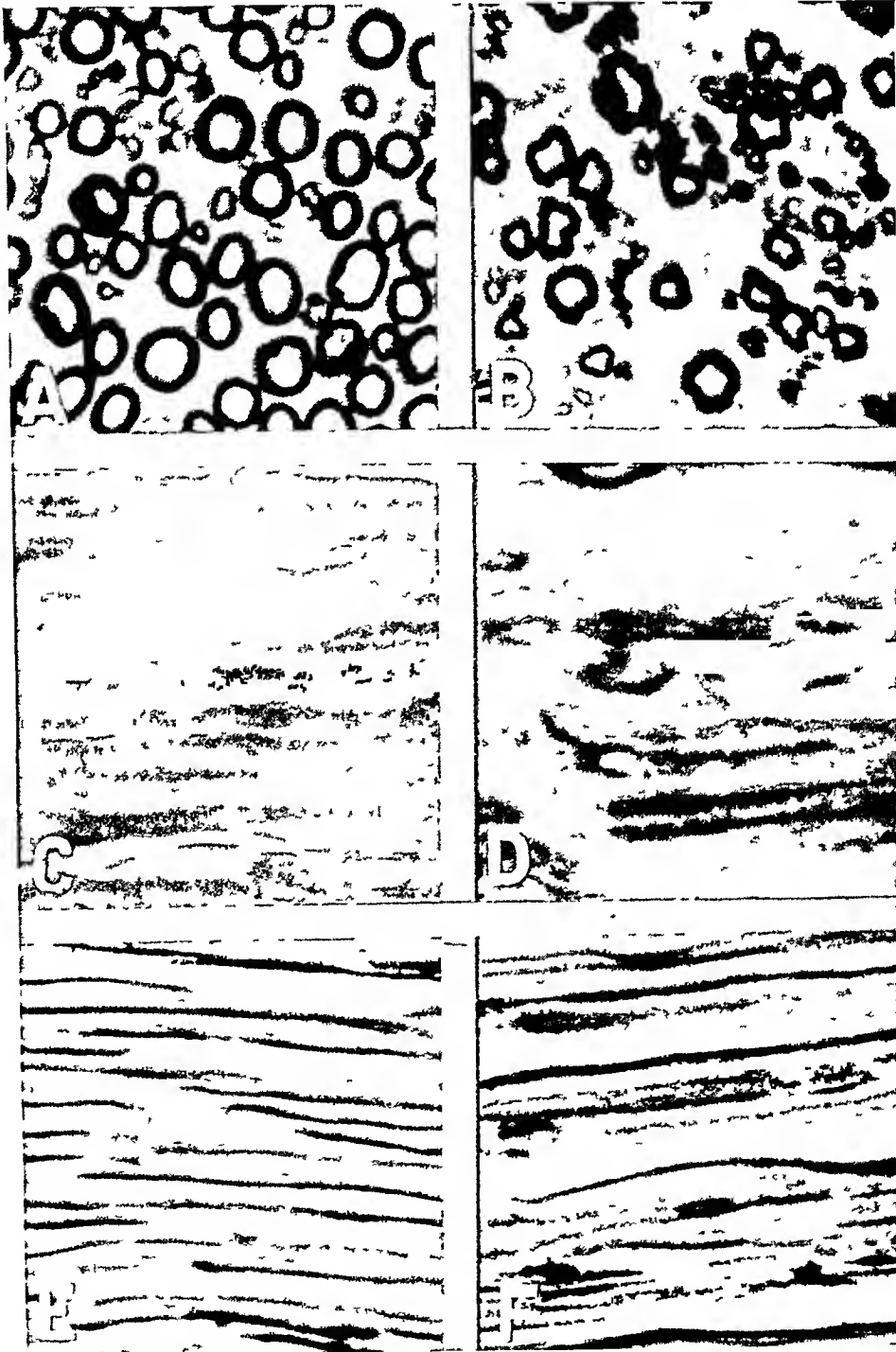


FIG 4—Photomicrographs ( $\times 525$ ) Thirty one days after cooling  
 A and C Cross and longitudinal sections of normal nerve stained with osmic acid  
 B and D Same of cooled nerve Note demyelination  
 E Longitudinal section of normal nerve stained with silver F Same of cooled nerve Note that some of the axones have disappeared completely

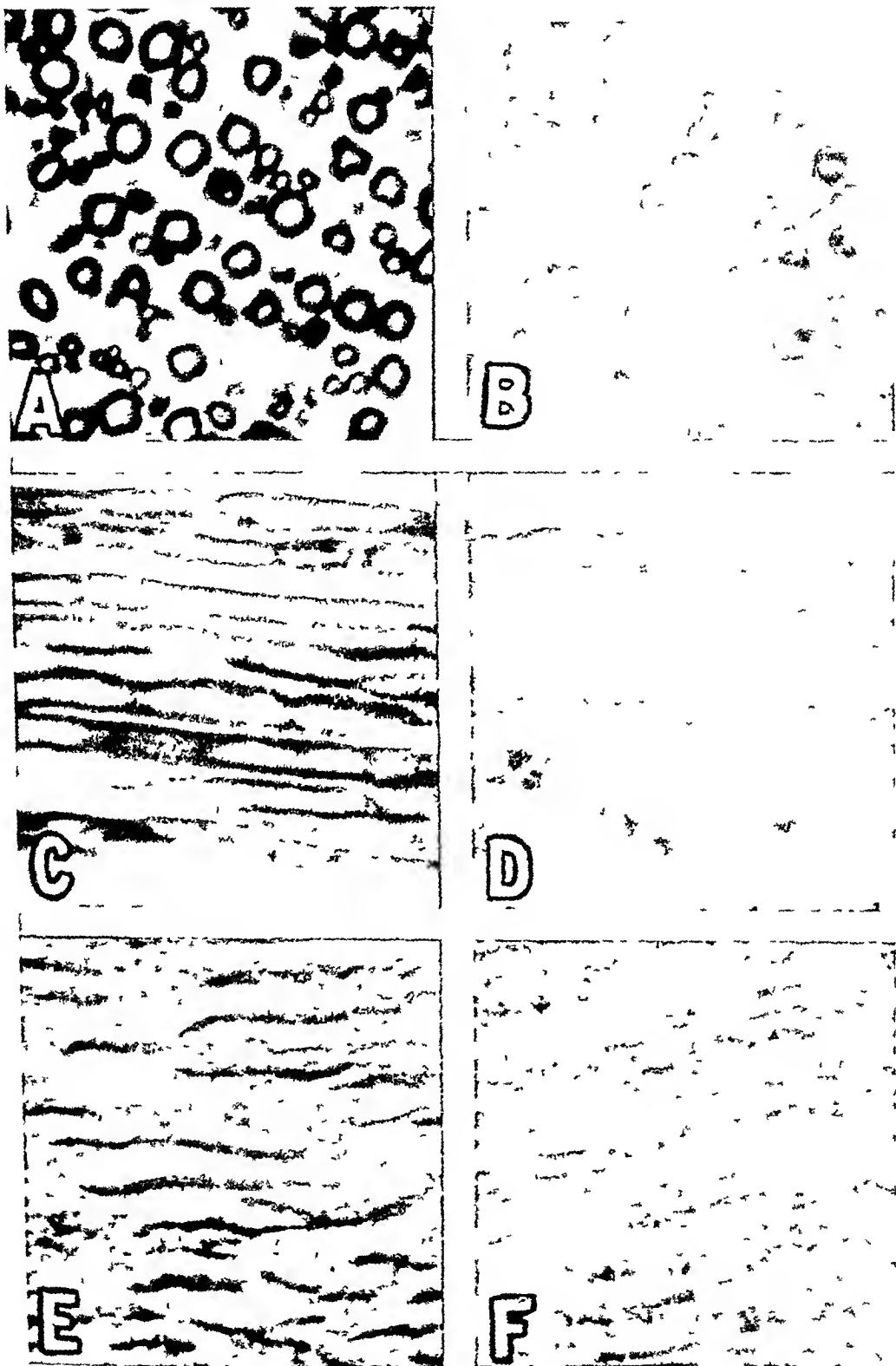


FIG 5—Photomicrographs (X 525) Forty three days after cooling  
A and C Cross and longitudinal sections of normal nerve stained with osmic acid  
B and D Same of cooled nerve Note almost complete disappearance of myelin  
E Longitudinal section of normal nerve stained with silver F Same of cooled nerve Note that most of the axons show marked degeneration This animal's leg exhibited the most marked swelling and paralysis of the entire group

direct injury of the tissues by cold, is responsible for the damage. This explanation is substantiated by the knowledge (a) that cooling results in prolonged sustained arteriolar constriction,<sup>4</sup> thus decreasing blood flow through and oxygenation of the part, and (b) that local anoxia results in marked increase in capillary permeability,<sup>5</sup> this latter factor thus also accounting for the edema which develops.

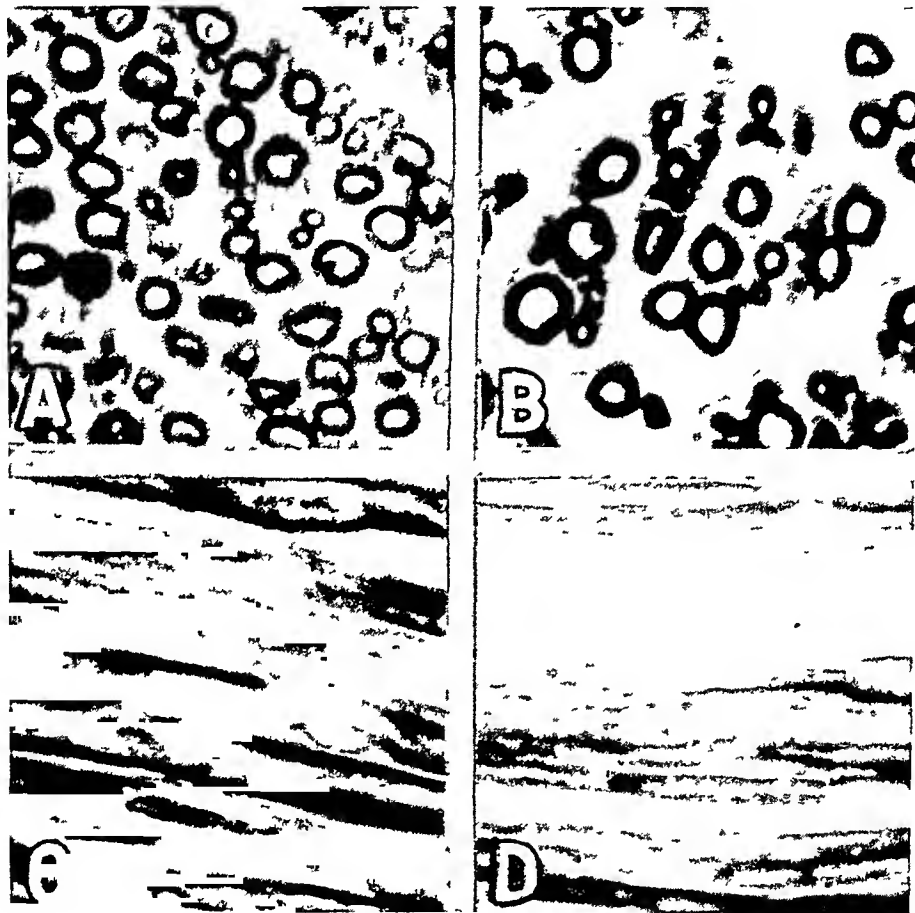


FIG 6—Photomicrographs (X 525) Ninety three days after cooling  
A and C Cross and longitudinal sections of normal nerve stained with osmic acid B and D Same of cooled nerve. This animal did not exhibit any demonstrable edema or obvious paralysis of the limb at any time, but degeneration of the nerve, as evidenced by disappearance of the myelin sheaths, is quite definite.

Few experimental studies of the effects of prolonged cooling have been reported. Smith, *et al*,<sup>6</sup> in 1915, studied "trench foot" by exposing rabbits' feet to cold, damp mud, and observed subacute inflammatory changes in the involved tissues, more particularly affecting the walls of the blood vessels. Results more similar to our own were obtained recently by Blackwood and Russell,<sup>7</sup> who immersed rats' tails in cold sea water for 48 to 96 hours and found that degeneration of both nerve and muscle fibers followed exposure. Clinical studies of sailors whose extremities have been exposed to cold and wet for prolonged periods reveal that long-standing vascular and neurotrophic disturbances may occur,<sup>8</sup> with pain, possibly due to scar contracture about small nerves,<sup>9</sup> a troublesome late feature.

It is clear from our studies that nerves are more susceptible to damage by cooling than are other structures, so that the extensive degenerative changes in other tissues seen clinically after long exposure to cold may in part be secondary to nerve damage. It is of interest to note that the loss of all types of nerve fibers is in keeping with the clinical evidence of hypofunction of the somatic motor and sensory nerves and of the autonomic fibers to blood vessels and sweat glands. The trophic changes in the tissues resulting from a loss of their innervating fibers, also, may play a part in the prolonged delay of wound healing known to occur in such tissues,<sup>2</sup> and further serve as a warning against the indiscriminate use of refrigeration as a therapeutic measure when the aim is other than amputation of the refrigerated part.

#### SUMMARY

Immersion of a dog's limb in water at 6° C for 96 hours results in edema and in temporary depression of sensory and motor function of the exposed extremity. It is followed by varying degrees of degeneration of the nerves in the cooled area, without demonstrable histologic changes occurring in other tissues. Although direct injury from the cold may play a minor rôle, the degenerative changes are regarded as being due essentially to ischemia of the part during and following the cooling period.

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## HYPERINSULINISM TREATED BY SUBTOTAL PANCREATECTOMY

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SINCE HARRIS<sup>7</sup> DESCRIPTION of the syndrome resulting from excessive secretion of insulin in 1924, many of the problems of this disease have been solved. The criteria for a diagnosis of islet cell adenoma and the indication for operation have been well stressed by Whipple<sup>11</sup>. The importance of considering all of the many causes of spontaneous hypoglycemia, and aids in the diagnosis of these, have been pointed out by Wilder,<sup>12</sup> Brunschwig,<sup>2</sup> and others. The use of a low carbohydrate diet for the diagnosis and management of some of these patients, as advocated by Waters,<sup>10</sup> has been a valuable contribution. The metabolic studies to determine the amount of carbohydrate, protein, and fat oxidized by these patients, as proposed by Conn,<sup>4</sup> have been an important addition to the study of the problem, and they are particularly useful in the study of questionable cases.

It has become apparent that functional hypoglycemia is a fairly common condition, while organic hyperinsulinism is quite rare. This fact makes the careful study of these patients, using every diagnostic aid available, in order to establish an etiologic diagnosis of the hypoglycemia, of the utmost importance.

When the "Whipple triad" of symptoms is present, surgical exploration of the pancreas is clearly indicated, and an islet tumor will be present in nearly all cases. This triad includes nervous system disorders, such as confusion, coma, convulsions, collapse coming on in the fasting state while the blood sugar level is 50 mg per 100 cc, or less, and the relief of symptoms by the administration of glucose. When the blood sugar does not fall to 50 mg per 100 cc during an attack, a careful search for causes other than islet adenoma must be made, and the etiologic factor may be found to be one of the following conditions (Table I).

When the blood sugar, during an attack, is above 50 mg per 100 cc a diet low in carbohydrate, 50 Gm, or less, and high in protein will often give relief from attacks, because while 50 per cent of the protein may yield dextrose, this conversion takes place at a slow, even rate, and this fact, as well as the slower absorption rate of protein, prevents any marked elevation of the blood sugar, which would, in turn, stimulate the pancreas.

It has been shown by Conn<sup>4</sup> that the glucose tolerance curve is influenced by the antecedent diet in normal people as well as those with hypoglycemia. We feel that a glucose tolerance test taken after a proper preparatory diet is of definite diagnostic value in cases of hypoglycemia. Organic and functional hyperinsulinism, both, characteristically, give a low

TABLE 1

ETIOLOGIC CLASSIFICATION OF SPONTANEOUS HYPOGLYCEMIA (CONN)

- I Organic—recognizable anatomic lesion
  - (a) Hyperinsulinism
    - 1 Pancreatic island cell carcinoma
    - 2 Pancreatic islet cell adenoma
    - 3 Generalized hypertrophy and hyperplasia of islands of Langerhans
  - (b) Hepatic disease
    - 1 Ascending infections—cholangitis
    - 2 Toxic hepatitis
    - 3 Diffuse carcinomatosis
    - 4 Fatty degeneration or metamorphosis
    - 5 Glycogenosis (von Gierke's disease)
  - (c) Pituitary hypofunction (anterior lobe)
    - 1 Destructive lesions (chromophilic tumors, cysts, etc.)
    - 2 Atrophy and degeneration (Simmonds' disease)
    - 3 Thyroid hypofunction—secondary to pituitary hypofunction
  - (d) Adrenal hypofunction (cortex)
    - Atrophy or destruction of cortex
  - (e) Central nervous system lesions (some interfere with nervous control of blood sugar)
- II Functional—no recognized anatomic lesion
  - (a) Hyperinsulinism (autonomic nervous system imbalance)
  - (b) Renal glycosuria
  - (c) Pregnancy and lactation

dextrose tolerance curve, and the organic cases usually have an abnormally low fasting level. Studies on the utilization of the injected glucose are especially indicated in borderline cases. The method which we have used is that suggested by Johnston,<sup>9</sup> of taking a basal metabolic rate prior to injection of glucose, and repeating the metabolism test at 0.5 hour, 1 hour, 2.5 hours, and 3 hours after the injection. Urine samples are examined for nitrogen and sugar if the proportion of carbohydrate, fat, and protein utilized are to be determined. The calculation from these studies of the respiratory quotient gives diagnostic information, and is also of benefit in following the patients postoperatively.

We feel that in patients who do not conform exactly to the "Whipple triad" and yet have the symptoms of hyperinsulinism, that these studies may aid in determining the advisability of performing a subtotal pancreatectomy. Two cases which had this operation are presented, one of which had extensive pre- and postoperative studies.

CASE REPORTS

Case 1—M. B., white, female, age 19, single, was first seen April 11, 1935. Her chief complaints were severe headaches and abdominal cramps. She also had a chronic cough, and had excessive weight gain. Roentgenograms of the chest and skull were both negative. Her basal metabolism rate was minus five. At this time the patient was taking one grain of thyroid daily. Fasting blood sugars were 78 and 99 mg. per cent.

In January, 1936, the patient admitted having had frequent attacks of weakness, sweating, tremor, and a mental reaction described as stuporous. This was associated

with the lack of food, and was quickly relieved by the ingestion of carbohydrate. At this time a glucose tolerance test was made and the results are shown in Chart 1. Blood sugar levels taken during attacks were from 55-60 mg. The family history was essentially negative, except for the occurrence of diabetes in an aunt on the maternal side. The patient's past history was noncontributory.

*Physical Examination*—The patient appeared to be a well-developed, slightly obese female, in no apparent distress. She was 5 feet, 5¾ inches in height, and 165 pounds in weight (estimated normal weight 138 pounds). Except for obesity and midepigastria

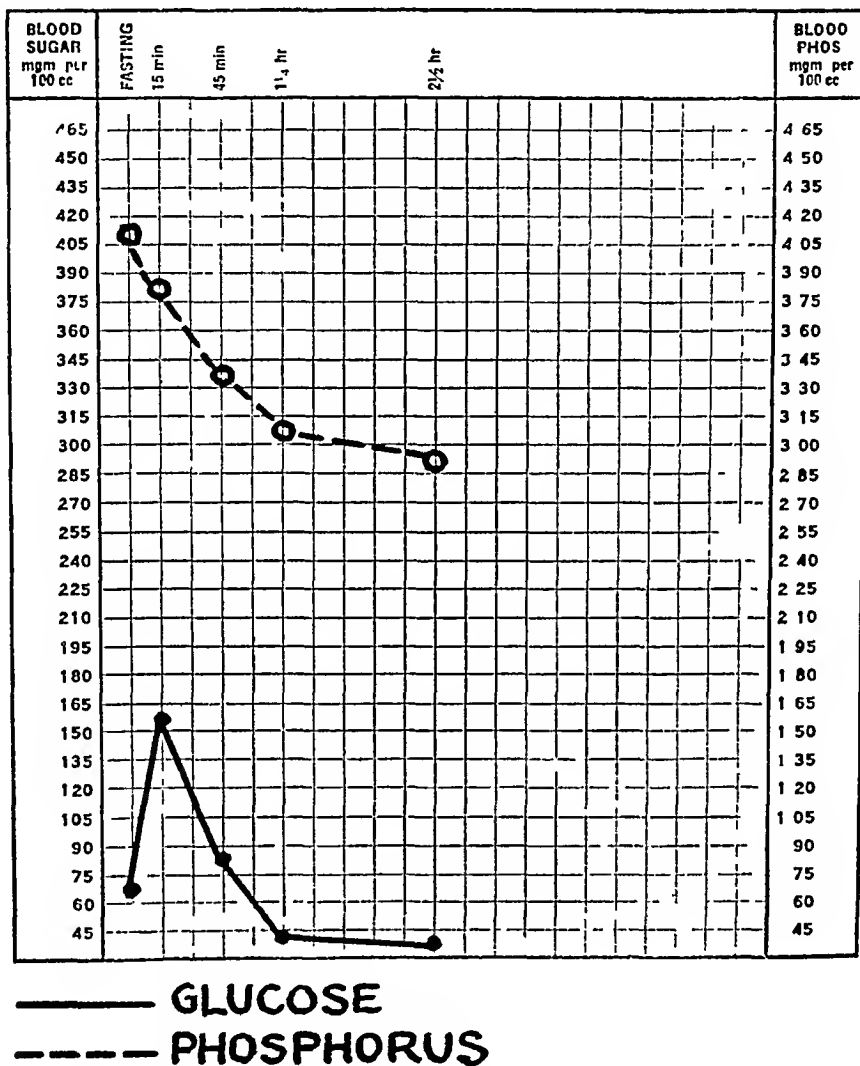


CHART 1—Case 1. Preoperative glucose tolerance and phosphorus curves.

tenderness on palpation the physical examination was normal. The chest was clear, the heart normal, blood pressure 118/74. Routine laboratory examinations, including uranalysis and blood count, were negative. *Clinical Diagnosis*: Spontaneous hypoglycemia.

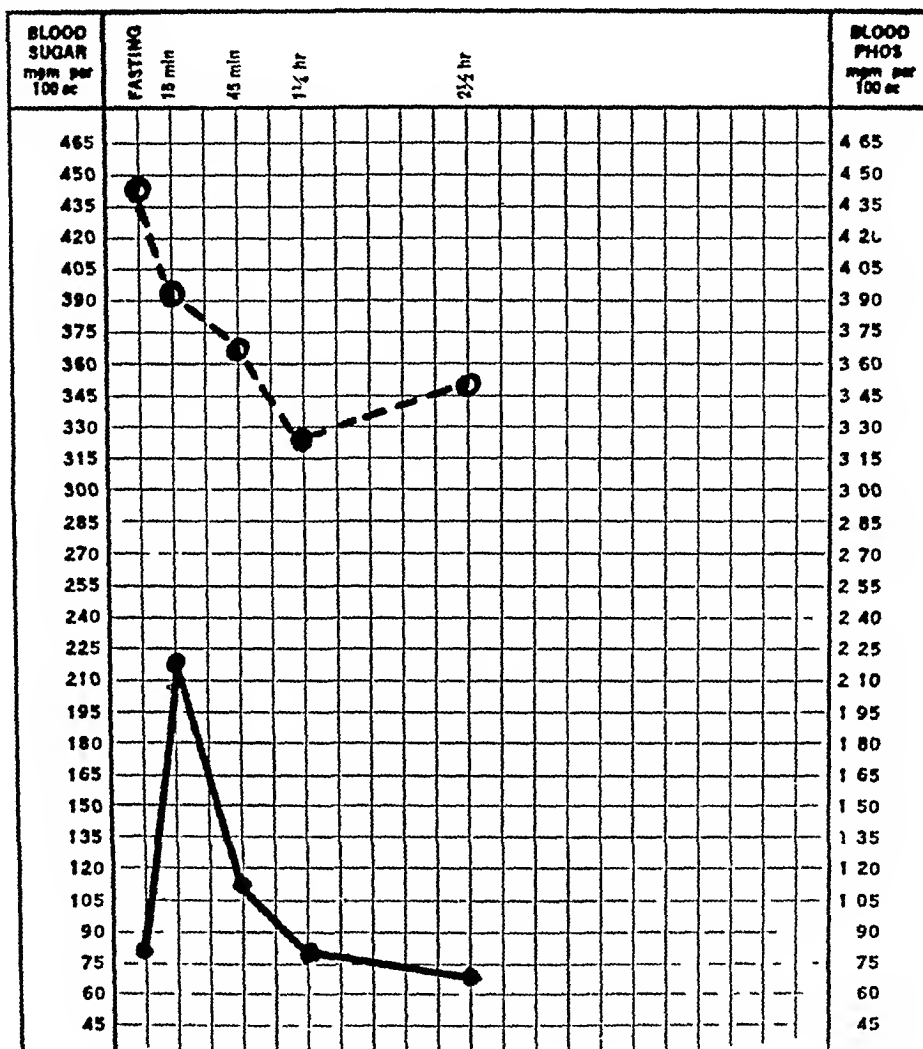
*Operation*—February 10, 1936. No tumor was found and, so, approximately two-thirds of the pancreas was removed. During the operation the patient was given 400 cc of glucose intravenously and 500 cc of whole blood. Hourly, postoperative blood sugar determinations were made and measured 250, 230, 230, 170, and 140 mg per cent, respectively.

Daily, fasting blood sugar determinations were made postoperatively and measured 135, 129, 111, 129, 105, 104, 75, 93, 96, 84, and 89, respectively. The postoperative

course was uneventful. The patient remained asymptomatic. The microscopic appearance of the gland was described as normal. Two months afterwards, a glucose tolerance was made and the results are shown in Chart 2.

The patient made an uneventful recovery. She has had no return of symptoms and blood sugar tests taken each year have remained normal. The pre- and postoperative respiratory quotients are shown in Chart 3.

**Case 2**—M. C., white, female, age 43, married, first entered the hospital, August 25, 1942, with complaints of nervousness, backache, low blood pressure, and sinus trouble.



—— GLUCOSE  
---- PHOSPHORUS

CHART 2—Case 1. Postoperative glucose tolerance and phosphorus curves.

Her first attacks of nervousness began in 1929, and were characterized by weakness, nervous irritability, excessive perspiration, and ravenous hunger, all occurring about three hours after meals, being worse after exercise, and which were relieved by eating, especially readily available carbohydrate. From her own experience she learned to eat four or five meals daily, yet lost weight gradually. Her attacks became progressively more severe, and soon began to occur in the early morning, and as early as one hour after meals. Further symptomatology included memory loss during attacks, mental cloudiness, speech difficulty, and visual disturbances. There was never any loss of consciousness. Personality changes made their appearance because of the patient's symptoms occurring when out with other people.



The patient's past history was essentially noncontributory, and consisted, in the main, of a number of unsuccessful operations designed to alleviate her symptomatology. The family history was of interest in that exactly similar symptoms were found in members of three successive generations—the father, one brother, and a daughter.

Physical examination was essentially normal. The patient was a well-developed and well-nourished white female, measuring 5 feet, 2 inches in height, and weighing

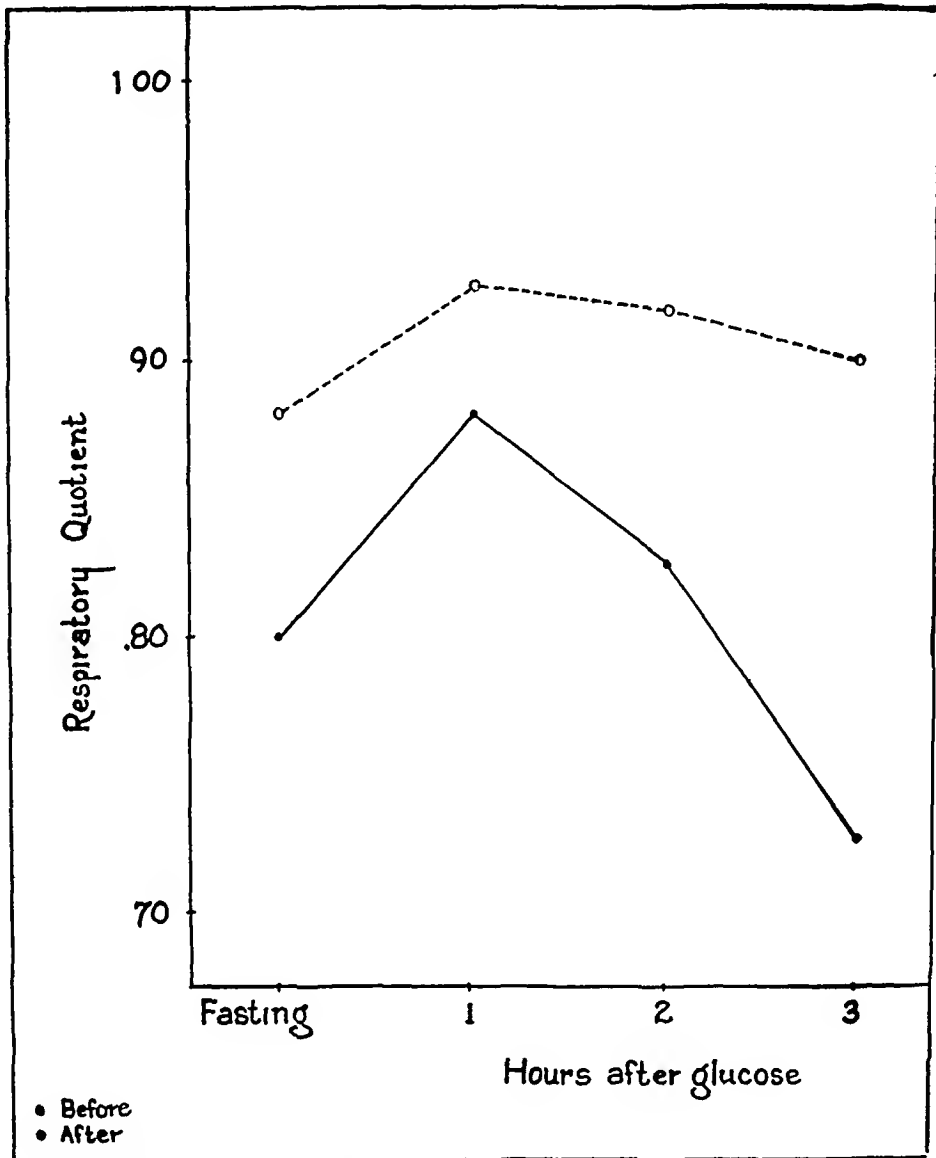
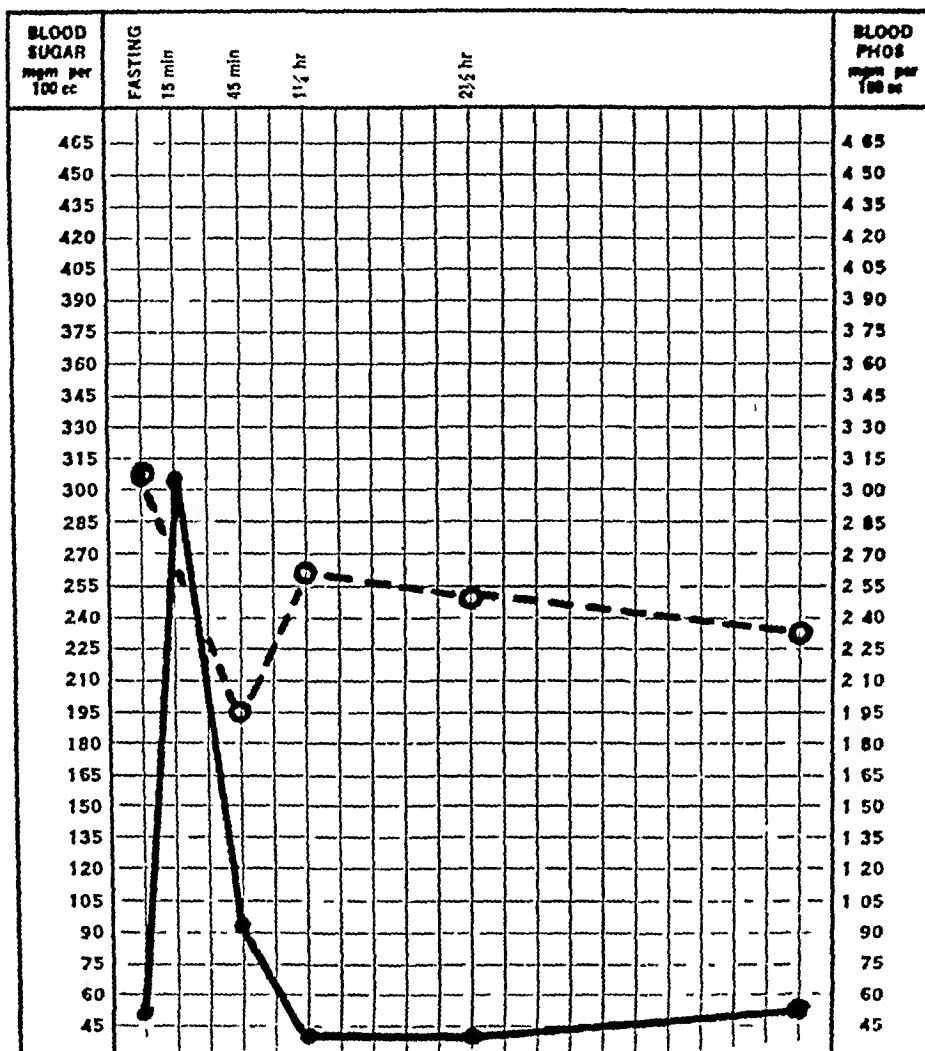


CHART 3—Case 1 Respiratory quotient before and after operation

119 pounds. The head and neck were normal. The chest was resonant, breath sounds normal. The heart was not enlarged, the rhythm regular, heart sounds normal, no murmurs heard. Blood pressure 95/60. Except for well healed postoperative scars, the abdomen presented no abnormalities. No masses were palpable. Examination of the extremities and pelvis was likewise normal.

**Laboratory Data**—The Kline exclusion test for syphilis was negative. The blood count was normal—hemoglobin 149 Gm, R B C 4,870,000, W B C 7,600, with 51 per cent polys. Urinalysis was negative, and the stool examination normal. Fasting blood sugars varied from 61 to 69 mg per cent. Other special examinations were also

made Blood diastase measured 130 Cephalin-cholesterol liver function test was one plus In the serial 2 mg-bromsulfalein test there was no retention of dye in 20 minutes The B M R was minus five, R Q 0.77 Twenty-four-hour urine for quantitative sugar was negative Fractional gastric analysis was normal, and except for poor "B" bile, transduodenal biliary drainage was negative Roentgenograms of the spine, skull, chest, gallbladder, stomach and duodenum were all normal Severe



—— GLUCOSE  
---- PHOSPHORUS

CHART 4—Case 2 Preoperative glucose tolerance and phosphorus curves

symptoms were induced in the fasting state by strenuous exertion, at which time the blood sugar measured 60 mg per cent One milligram of epinephrine was given subcutaneously, with relief of all symptoms within 15 minutes, when another blood sugar specimen measured 73 mg per cent

The patient was discharged, September 2, 1942, on a high protein, low carbohydrate diet, with 5-6 meals daily, and thyroid extract grain 0.5 daily Despite this program, symptoms became gradually more severe, and the patient was readmitted January 24, 1943, and, again, on April 11, 1943 Glucose tolerance tests were repeated on each of these occasions, and the last one had to be terminated at the end of 1.75 hours because of the severity of the hypoglycemic reaction (Chart 4) On this latter occasion further laboratory observations were made The blood N P M measured 26.5 mg per cent,

blood sodium 332, blood potassium 175 The B M R was now plus four, the R Q 080 The cephalin-cholesterol test was plus three, and the intravenous hippuric acid test measured 098 Gm Prothrombin was 100 per cent

The patient was transferred to the Surgical Service for operation, April 22, 1943 In preparation for operation she was given 500 cc of 10 per cent glucose intravenously This was followed in 15 hours by a reaction which required the injection of 50 cc of 50 per cent glucose for relief During the operation she was given 500 cc of 10 per cent glucose and 500 cc of whole blood The tail of the pancreas was found to be hyperplastic and firm, but no adenoma could be found, and approximately five-sixths

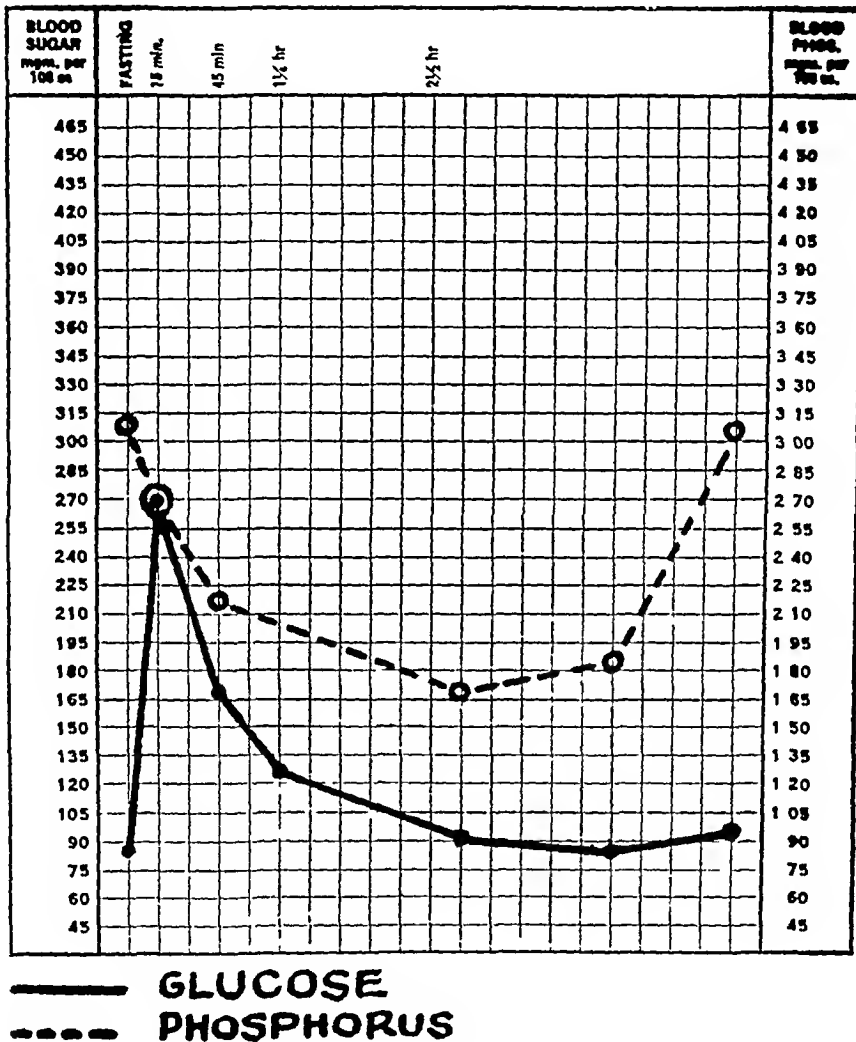


CHART 5—Case 2 Postoperative glucose tolerance and phosphorus curves

of the gland was resected The microscopic examination of the gland was described as normal Postoperative blood sugar determinations were made hourly, and measured 108, 91, 85, 109, 127, 131, 145, 112, 132, 98 respectively A glucose tolerance test was made 24 hours postoperatively, and the results are shown in Chart 5 Daily blood sugars varied between 80 and 100 mg per cent Postoperatively, the serum cholesterol level was 135 mg per cent and the total plasma fat 450 Analysis of stool specimens for fatty acids, neutral fat, and total fat, after the ingestion of a high fat meal, was within normal limits, showing satisfactory function with regard to the pancreatic external secretions

The patient's postoperative course was completely uneventful. She is at present enjoying excellent health and has had no return of symptoms. The fasting blood sugar level has been between 80-100 mg per cent since the operation.

**DISCUSSION**—The failure to find an islet adenoma in these cases was at first disappointing, but the excellent results obtained following subtotal pancreatectomy has led us to agree with David<sup>5</sup> and Womack,<sup>13</sup> that this is the procedure of choice when no adenoma can be found, after a careful search of the pancreas and the usual sites where heterotopic pancreatic tissue sometimes occurs.<sup>8</sup> While excellent results may be expected following a subtotal resection, we would again like to caution against anything less than a subtotal resection. The function which the pancreas plays in digestion was found not to be affected significantly when four-fifths of the gland had been removed.

The use of a high protein, low carbohydrate diet for a preoperative trial is excellent. We have, in some cases, experienced difficulty in getting patients to refrain from the ingestion of some carbohydrate when the prodromal symptoms of an attack appear. The symptoms are quite unpleasant, and the patients' complete confidence is necessary to keep them from escaping this by taking a little carbohydrate, which they have found relieves them, at least temporarily.

Hyperplasia of the islet cells is difficult to be sure of pathologically, just as it is difficult to tell which tumors are benign and which are malignant. This difficulty has previously been expressed by Womack,<sup>13</sup> and also by Fiantz.<sup>6</sup> The microscopic appearance of the two cases here reported was described as normal.

#### SUMMARY

Two additional cases presenting the syndrome of spontaneous hypoglycemia, and in which no islet tumor could be found, are reported. The very satisfactory results obtained following subtotal resection in these cases makes us confident that no actual islet tumor existed. Emphasis is again directed to the fact that a large amount of pancreas must be resected in these cases.

The study of metabolism of glucose in these patients after they have been on a standard preparatory diet may be of benefit in a diagnostic way and in evaluating the results of treatment.

The removal of a large amount of the pancreas does not seem to cause any subsequent digestive or metabolic disturbance.

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# STELLATE GANGLION BLOCK

## A NEW ANTERIOR APPROACH

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THE TEMPORARY INTERRUPTION of sympathetic impulses by the injection of procaine hydrochloride about the sympathetic ganglia is a recommended therapeutic procedure in acute vascular injuries <sup>1, 2, 3, 4, 5, 6, 7, 8</sup> The purpose of the injection is to overcome secondary spasm of the collateral vessels. Reflexes, arising in the damaged segment of a blood vessel and transmitted by the sympathetic nervous system, give rise to this spasm. In time of war, with the great increase in the number of patients suffering from vascular injuries of the extremities, a simple technic for the injection of the sympathetic ganglia is desirable. This is especially true when one recognizes that the majority of these cases will, of necessity, be cared for by physicians whose experience in this field of surgery is more or less limited. The technic for injecting the lumbar sympathetics is not difficult. The prominent landmarks and the absence of important structures in the immediate vicinity of this portion of the sympathetic chain make this procedure relatively simple. This is not true of the sympathetic supply to the upper extremity which is generally interrupted by infiltration in the region of the stellate ganglion. This structure lies close to the great vessels of the neck (Fig 1), and is intimately related to the dome of the pleura. Recently, a soldier was admitted to this hospital suffering from ischemia of the upper extremity secondary to trauma of the brachial artery. Repeated attempts by various members of the surgical staff to interrupt the sympathetic supply to this extremity were unsuccessful. The purpose of this report is to present a technic for stellate ganglion block, which was developed as a result of this experience, and which has proven successful in our hands.

Two approaches to the stellate ganglion have been generally employed. One technic employs a posterior paravertebral route and is essentially the method described by Labat,<sup>9</sup> in 1924. The "occasional" operator finds it difficult to advance the tip of the needle forward along the vertebral body sufficiently to contact the sympathetic chain and at the same time avoid the pleural cavity. The parietal pleura is in intimate contact with the thoracic vertebrae, and the advancing needle must pass between them. With the second method the stellate ganglion is injected by inserting the needle anteriorly just above the clavicle <sup>10, 11</sup>. In the latter technic failure to interrupt the sympathetic pathway has been frequent. The tip of the needle often enters one of the great vessels of the neck and on changing the direction sufficiently to avoid these structures contact with the vertebra cannot be made. In addition, with the cutaneous puncture site just above the

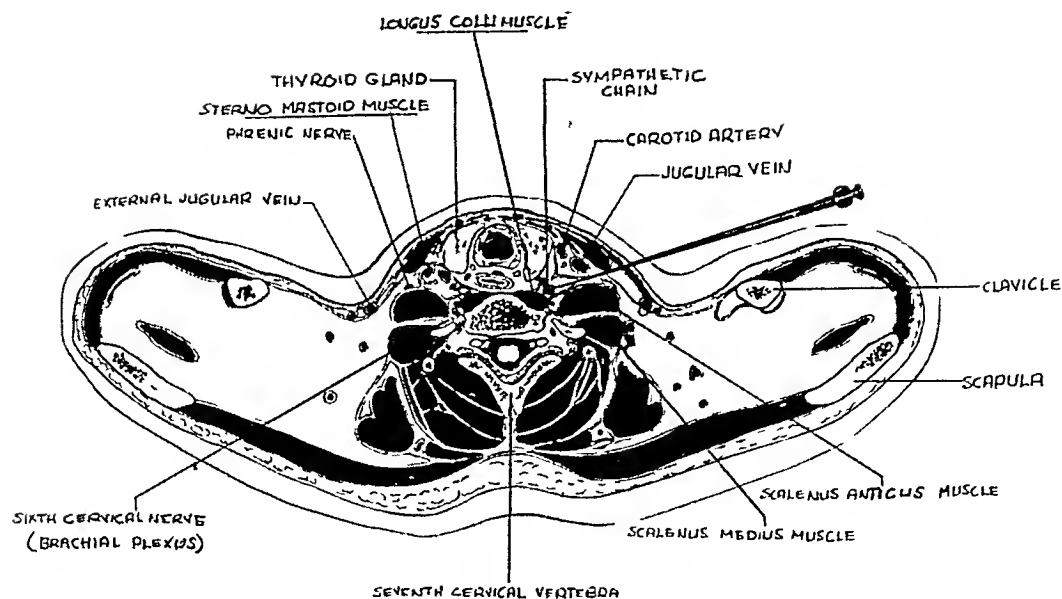


FIG 1—Anatomic drawing of a cross section of the neck at the level of the cricoid cartilage with the needle directed posteriorly and medially at an angle of 15 degrees with the ventral surface of the scalenus anticus muscle

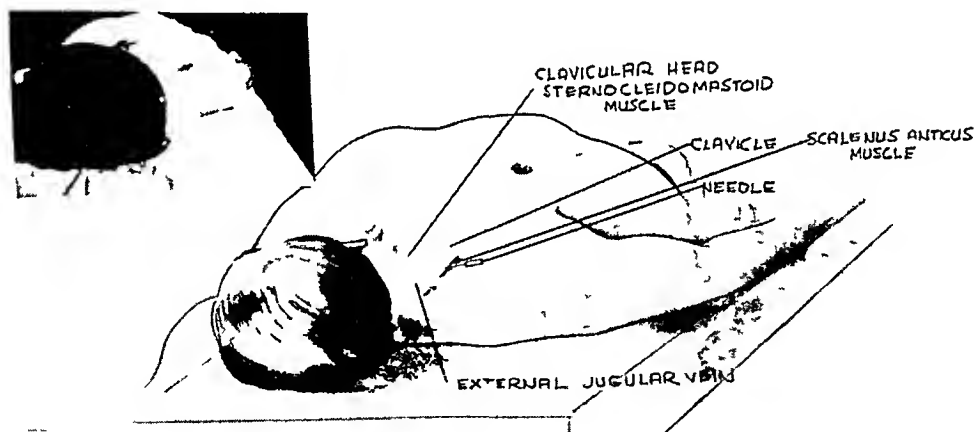


FIG 2—Sketch of patient with needle in place illustrating its relationship to the important landmarks. Inset, photograph of the same patient

*Technic of Stellate Ganglion Block by the Proposed Anterior Approach.* The patient is placed in a supine position on a firm bed. The skin is surgically prepared and the landmarks, i.e. the cricoid cartilage and scalenus anticus muscle, are identified by palpation. The latter is more easily felt if the patient's face is turned toward the opposite side and the neck extended. A thin pillow under the patient's shoulders gives adequate extension of the neck. The external jugular vein crosses the lateral edge of the scalenus anticus muscle at the level of the puncture site (cricoid cartilage), and is an aid to its identification. A wheal of novocaine is made at the point of puncture, i.e. at the edge of the scalenus anticus muscle, and in the same place as the cricoid cartilage. A fine lumbar puncture needle is introduced through this wheal and directed posteriorly and medially in line with the cricoid cartilage at a 5 to 15 degree angle with the horizontal plane (bed). The point of the needle contacts the antero-lateral surface of the 7th cervical vertebra at a depth of 3.5 to 6 cm. If contact with the vertebra is not made, the needle should be withdrawn and reinserted with the tip directed more posteriorly. The needle is withdrawn from immediate contact with the vertebra to clear the point of the periosteum prior to injection. Before the novocaine solution is introduced, the needle should be aspirated to ascertain that it does not lie within a blood vessel or the subarachnoid space. It is possible to enter the latter through one of the vertebral foramina. Ten cubic centimeters of a 2% novocaine solution are then injected. There is sufficient spread of the solution through the fascial planes to block completely the sympathetic supply to the upper extremity. Evidence that the solution has been properly placed is the development of a Horner's syndrome, i.e. ptosis of the upper lid, slight elevation of the lower lid with narrowing of the palpebral fissure, enophthalmos, contracted pupil and anhidrosis. In addition to the above changes there is a marked congestion of the conjunctiva due to dilatation of its vessels. This phenomenon usually occurs within ten minutes after the injection.

clavicle the cervical projection of the apex of the lung is frequently injured, resulting in the development of pneumothorax. Although this complication usually is not followed by serious sequelae, it should be avoided.

The stellate ganglion, formed by the fusion of the inferior cervical and first dorsal sympathetic ganglia, lies on the anterolateral surface of the first thoracic and 7th cervical vertebrae between the head of the first rib and the vertebral artery. Frequently it exhibits a length of 2.5 cm. The cervical sympathetic trunk immediately above the ganglion lies on the deep fascia of the neck covering the anterior surface of the longus capitis and longus colli muscles (Fig. 1). This fascia is continuous with, and in the same plane as, the deep fascia covering the anterior surface of the anterior scalene muscle. The phrenic nerve which lies on the deep fascia covering the anterior scalene muscle, therefore, lies lateral to, but in the same plane as, the cervical sympathetic trunk. The internal jugular vein, carotid artery, and vagus nerve, enclosed in their fascial sheath, lie anterior to these muscles. The dome of the pleura and apex of the lung extend well above the clavicle anteriorly and to the lower edge of the first rib posteriorly. Dissections of the neck performed upon cadavers have confirmed the above anatomic relations. With the patient supine, it was found that if an ordinary spinal puncture needle was inserted at the level of, and directed toward, the cricoid cartilage, it would pass above the apex of the lung. If this puncture site was at the lateral edge of the scalenus anticus muscle and the needle was inserted with the point directed posteriorly so that the shaft made an angle of from 5 to 15 degrees with the horizontal plane, the needle would pass behind the great vessels and contact the body of the 7th cervical vertebra (Figs. 1 and 3). Frequently the point of the needle was found in contact with the stellate ganglion.

Clinical application of this approach was successful in 67 out of 70 attempts (95.7 per cent). Furthermore, these injections have been carried out by four different medical officers, which is supporting evidence in favor of the accuracy and simplicity of the procedure.

Complications arising as a result of the injection of the stellate ganglion by this approach have been few. The patients almost universally complain of pain when the deep fascia near the vertebral column is pierced, but this discomfort is only transitory. The novocaine solution, in addition to surrounding the sympathetic chain, has occasionally spread to the spinal nerves resulting in temporary hypoesthesia and paresis of the corresponding upper extremity. The seventh and eighth cervical and first thoracic roots are the ones usually involved. Fluoroscopic examination of our patients, following the injection, have failed to reveal diaphragmatic paralysis as a result of spread of the solution to the phrenic nerve. With the phrenic nerve and cervical sympathetic trunk lying in the same fascial plane such diffusion could easily occur. The needle entered the subarachnoid space in one case as shown by aspiration of spinal fluid. It should be noted that the needle passed through the intervertebral foramen without causing pain. The



needle was withdrawn, replaced, and the stellate ganglion injected. No untoward symptoms were noted on this patient. Although procaine is a relatively nontoxic drug, the danger of a toxic reaction must be constantly borne in mind. This danger can be minimized, according to Weiss,<sup>12</sup> by

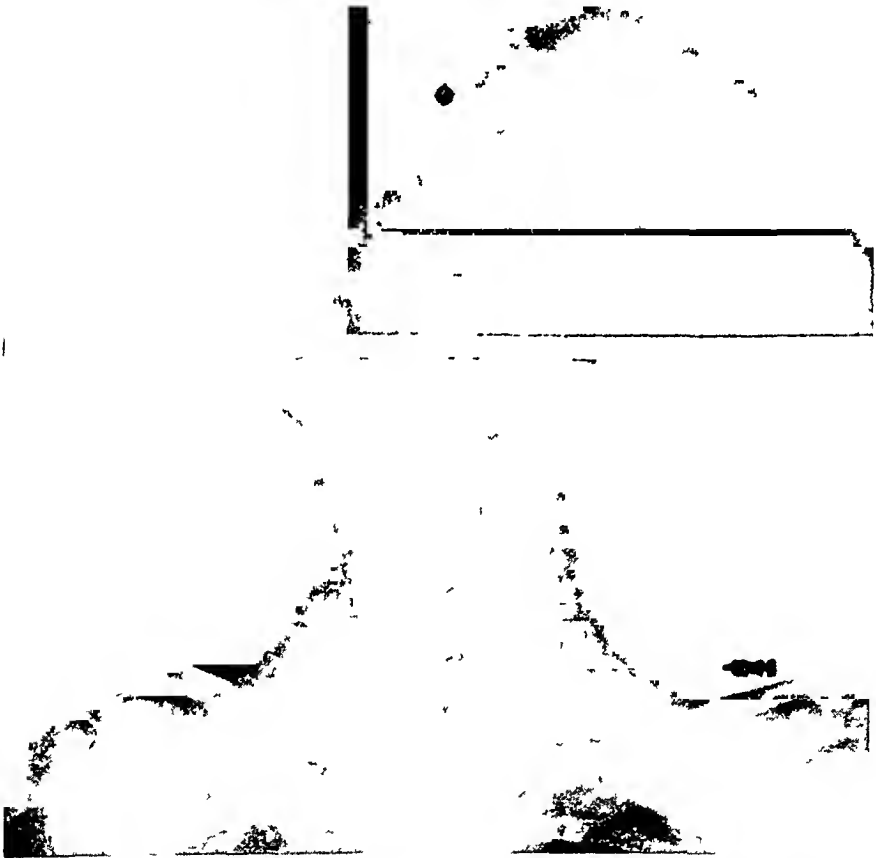


FIG 3.—Lateral and interoposterior x rays of a patient with the needle in place. The tip of the needle can be seen to be in the anatomical location of the stellate ganglion, *i e*, at the inferior border of the body of the 7th cervical vertebra. The needle is also seen to be above the apical portion of the lung.

the preliminary use of one of the barbiturates. This has been done in all of our cases and no evidence of procaine reaction has been noted.

#### SUMMARY

1. An anterior approach for injection of the stellate ganglion has been described.

2. The complications encountered with this method have been briefly discussed.

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# CONGENITAL ATRESIA OF THE ESOPHAGUS WITH TRACHEO-ESOPHAGEAL FISTULA

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DURING THE LAST THREE YEARS seven infants with congenital atresia of the esophagus were admitted to the Vanderbilt University Hospital. A tracheo-esophageal fistula, Vogt's type 3B<sup>1</sup> was present in each case. All of these patients were operated upon. The operative procedures have varied but in all cases the fistula has been exposed at operation. An end-to-end anastomosis of the segments was attempted in three cases and it was possible to bring the ends of the segments together in two of them. One patient survived and is living. This child is six months old.

A summary of the cases is presented in Table I, and the one case in which a successful anastomosis was effected is reported in detail.

**Case Report**—R. L. C., male, born November 28, 1943, in the Vanderbilt University Hospital, at term. He was the first child of a healthy and normal mother, age 33. At birth the infant weighed 6 lbs., 7.75 ounces. He breathed spontaneously, and physical examination revealed no abnormalities. Thirty-six hours after birth it was noted that the child had an unusually large amount of mucous in his mouth and throat, and 56 hours after birth the following note was made by the Pediatric intern: "Baby having a large amount of mucous and is vomiting practically all fluids offered. Believe this baby should be investigated for possibility of tracheo-esophageal fistula." The infant was given 50 cc of blood plasma and 50 cc of 10 per cent glucose intravenously and 200 cc of normal saline solution subcutaneously, and a catheter was passed into the pharynx. The tube could be inserted for a distance of only six inches, where it met an obstruction. The infant was then taken to the Roentgenologic Department, where a swallow of radiopaque oil revealed the esophagus to end in a blind pouch about two inches below its origin. The presence of large amounts of gas in the gastro-intestinal tract confirmed the diagnosis of congenital atresia of the esophagus, with tracheo-esophageal fistula.

The patient was transferred to the Surgical Service. At this time his weight was 5 lbs. 12.5 ounces. The breath sounds were rough throughout both lung fields but there was no evidence of consolidation. The patient showed no evidence of dehydration.

He was given 25 cc of blood plasma and 25 cc of 10 per cent glucose solution intravenously, and 100 cc of normal saline subcutaneously, and taken to the operating room 84 hours after birth.

**Operation**—The skin of the posterior neck and back was prepared with soap, sterile water and alcohol. The skin and subcutaneous tissues about the line of incision were infiltrated with 0.5 per cent procaine solution. No other anesthesia was used throughout the procedure.

An incision about six centimeters long was made about one centimeter to the left of the spinous processes, extending between the spine and the border of the scapula. The 3rd, 4th, and 5th ribs were divided and segments of the ribs about one centimeter in length were excised. The ribs were retracted forward. The intercostal muscles were divided and the parietal pleura was carefully stripped from the surface of the transverse processes and the spine. This dissection was carried down until the mediastinum

The author wishes to express his appreciation to Dr. Mary Clark of the Department of Pediatrics, for her untiring efforts in the postoperative care of this patient.

# ATRESIA OF ESOPHAGUS

TABLE I  
SUMMARY OF CASES

Case No and Admission Date	Age (Days) at Operation	Time (Hours) of Delay in Operation Following Diagnosis	Operative Procedure	Anesthetic	Duration of Life After Operation	Remarks
1 9-25-41	4	24	Rt 6th intercostal space transpleural approach Lower segment ligated at fistula, divided and Cervical esophagostomy	Ether vapor (Positive pres- sure)	Expired on op- erating table during closure of wound	Lower segment very small at its upper end Fistula posterior surface of trachea just above carina Autopsy Early bilateral bronchopneumonia
2 10 22-41	5	24	10-23-41 Rt paravertebral, retropleural ap- proach Lower segment exteriorized as above Small opening made through pleura during op- eration 10-25-41 Cervical esophagostomy	Drop ether (open mask)	10 days	Lower segment very small at its upper end Fistula at the carina Imperforate anus and Autopsy not performed
3 9 4 42	8	36	Rt paravertebral retropleural approach Lower segment visualized Patient stopped breathing and condition so poor ligation was not accom- plished Wound closed Gastrostomy performed	Drop ether (open mask)	3 5 hours	Lower segment fairly well developed Fistula high posterior wall of trachea Upper seg- ment long Autopsy Bilateral bronchopneumonia Ab- scess left upper lobe
4 1 16 43	6	6	4-16-43 Fistula not exposed at first operation Cervical esophagostomy Ligation of esophagus at hiatus through abdominal approach Gas- trostomy 5-11-43 Lt 8th intercostal space, transpleural approach Lower segment esopha- gus excised, after ligation fistula Diaphragm in- cised and stump of esophagus turned into stomach	Drop ether (open mask) 5-11-43 Ether vapor and oxygen (Positive pressure)	28 days after 1st operation	Lower segment very small at its upper end Fistula posterior trachea just above the carina Autopsy Gastropleural fistula Empyema
5 9 20 43	7	24	High Rt paravertebral, retropleural approach Fistula ligated Attempted end-to-end anasto- mosis Sutures pulled out Wound closed Cervi- cal esophagostomy Abdomen opened Cervi- segment esophagus divided at hiatus Lower stump turned into stomach Gastrostomy	0 5% novocaine 12 hours	3 days after 2nd operation	Upper end of lower segment small and delicate the carina Autopsy not performed
6 11-28 43	3	12	Reported in detail Left posterior retropleural approach	0 5% novocaine 30 hours		Upper segment very short Upper end lower segment small Fistula posterior, 5 mm Autopsy Empyema right mediastinitis Segments separated posteriorly
7 1-27 44	2	24	High right paravertebral approach ligated End to-end anastomosis over No 14 F catheter Same procedure as described for Case 6 Extreme tension on suture line posteriorly Wound closed without drainage	0 5% novocaine		

was reached. Three upper intercostal arteries were divided between clamps and were ligated with fine silk. In this way the arch and upper portion of the descending aorta could be mobilized and retracted forward. After a rather lengthy search, the upper blind pouch of the esophagus was located and its lower portion was freed. A traction suture of silk was placed through the lower end of this pouch. The trachea was then exposed. The right and left main stem bronchi were identified and the lower segment of the esophagus was found attached to the carina (Fig 1). It was freed and a ligature of fine silk was placed around the lower end of the esophagus close to the carina. A No 10 F catheter was placed through the infant's nose into the upper segment of the esophagus. A very small opening was then made through the lower end of the

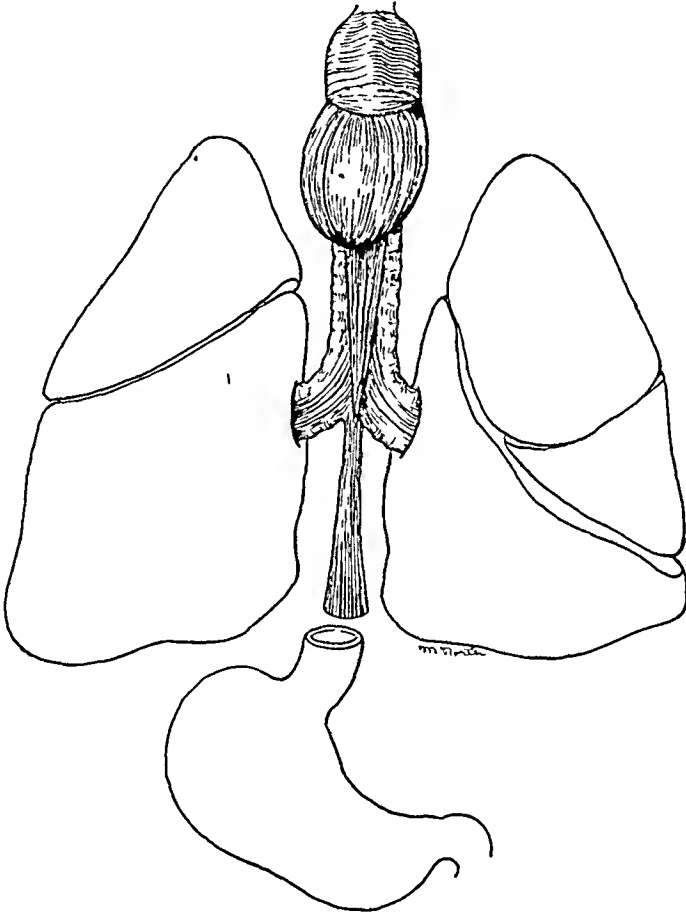


FIG 1—Sketch showing the deformity observed in Case 6 (Posterior view)

blind pouch of the esophagus. The catheter was passed through this opening into the wound. The exposed portion of the lower segment of the esophagus was of extremely small caliber and had a very thin wall. With the scissors a small nick was made in the side of the wall of the lower segment about five millimeters below the silk ligature (Fig 2). The end of the catheter was then threaded through this opening into the lumen of the esophagus and passed downward for a distance of about six inches. Another ligature of fine silk was then placed around the esophagus and was tied tightly over the lower segment of the esophagus and the enclosed rubber catheter about three millimeters below the opening through which the catheter was placed (Fig 3). The lower segment of the esophagus was then divided completely between the two ligatures. Slight upward traction was placed on the catheter. In this way the lower

## ATRESIA OF ESOPHAGUS

segment could be pulled upward a little way. Interrupted fine silk sutures were placed in the wall of the upper segment and through the wall of the lower segment below the ligature so that when these sutures were tied the lower segment was inbricated into the upper segment (Fig 4). Interrupted fine silk sutures were placed in this manner around the entire circumference of the esophagus. Toward the end of this procedure a small hole was inadvertently made in the parietal pleura, so that a pneumothorax was created.

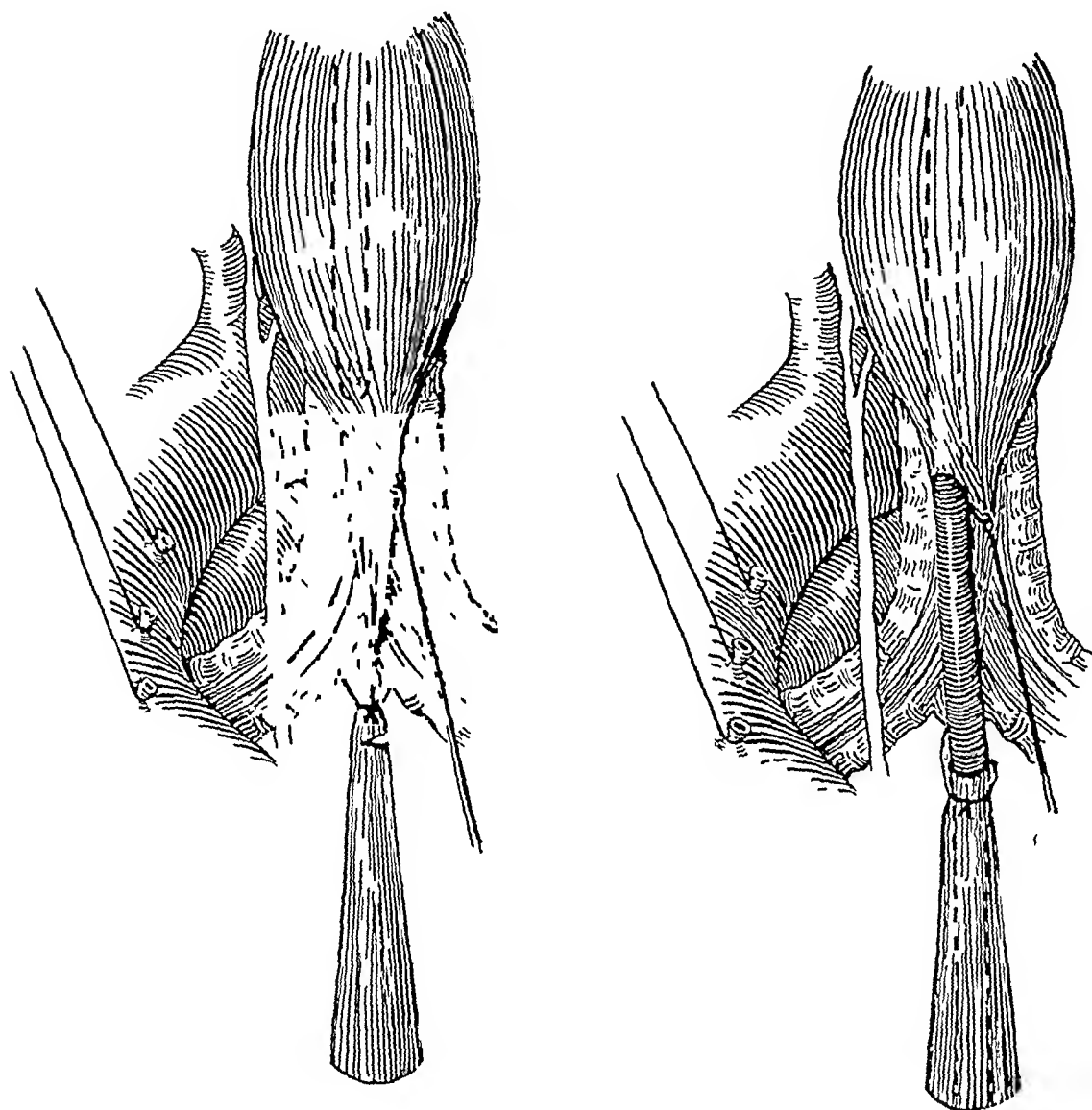


FIG 2—The upper intercostal arteries have been divided between ligatures and the arch of the aorta displaced. A traction suture fixes the end of the upper pouch, into which has been passed a small catheter. The lower segment has been ligated just below the fistula and an opening has been made through the side of the wall of the lower segment.

FIG 3—The catheter has been passed through a small opening at the lower end of the upper pouch and through the opening in the wall of the lower segment, downward into the stomach. The lower segment has not yet been completely divided.

A small rubber tissue wick was placed into the wound and its end was left about one centimeter lateral to the esophagus. The surface of the wound was dusted with two grams of sulfanilamide powder. The soft tissues of the wound were brought together and sutured in layers with interrupted fine silk sutures. Traction on the catheter was maintained while closure of the wound was effected. A Logan's bow was applied to the child's face and the catheter was strapped to the bow with adhesive in such a way as to maintain the traction which had been applied to the catheter.

The child was given oxygen throughout the procedure. There were short periods of cyanosis but at the end of the procedure the child's general appearance was fairly good.

*Postoperative Course*—Immediately upon return to the ward, the patient was placed in a warm incubator crib in the Trendelenburg position. Oxygen was given by means of a mask placed near the face. Twenty cubic centimeters of blood plasma and 20 cc of 10 per cent glucose solution were administered intravenously, and 60 cc of normal saline were given subcutaneously. Fluids were administered in this manner every four hours during the next two days.

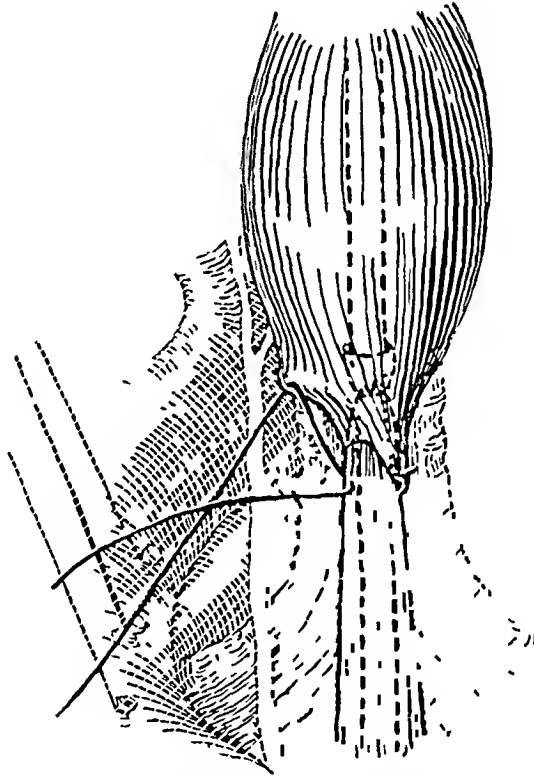


FIG 4—The long segment has been completely divided and is being imbricated into the upper segment. Considerable traction has been placed on the catheter to pull the lower segment upward slightly.

Forty-eight hours after the operation it was noted that there was no tension on the catheter, and that it could be moved up and down through the esophagus.

Feedings of 10 per cent glucose every two hours were begun, through the catheter, 48 hours after operation. Two days later he was begun on 15 cc of skimmed milk formula every two hours.

Occasional episodes of cyanosis followed the accumulation of mucous in the mouth and throat. Scattered moist râles were heard over both lung fields, and a roentgenogram of the chest, made seven days after operation, showed some scattered, hazy areas of decreased penetration throughout both lung bases.

On the seventh postoperative day the esophageal catheter became obstructed, and despite repeated attempts it could not be reopened. It was thought to be inadvisable to remove the catheter because of the belief that a stricture at the site of anastomosis was almost certain to occur. Gastrostomy was performed and small feedings of formula and 10 per cent glucose solution were begun 24 hours after operation. Feedings were

gradually increased in amount until the normal calculated quantity of formula was given, in 12 daily feedings, ten days following gastrostomy

During this period of time the esophageal catheter was left in place. Two weeks after gastrostomy was performed an attempt was made to deliver the end of the catheter through the gastrostomy wound. The tube could not be found, even by direct vision through a small esophagoscope inserted through the gastrostomy wound. Repeated attempts were made to find the catheter during the succeeding ten days, when this was accomplished by means of a simple hooked probe. A braided silk string was tied to the end of the catheter, the catheter removed through the nose and the string left through the esophagus.

Dilatations were begun with a No. 12 F retrograde bougie the following day, five weeks after the original operation. Five days later a No. 16 F bougie was passed with little resistance. The child then suddenly developed a severe diarrhea. Innoculation of the corneae of a rabbit revealed a virus, recently described by Buddingh and Dodd<sup>2</sup> as the cause of severe stomatitis and diarrhea in infants. Cultures from the mouth of the intern caring for the patient revealed the presence of the virus and indicated the source of the infection.

Dilatations were not carried out then for ten days. During this time the patient's diarrhea had become very severe. In spite of the frequent administration of blood plasma the patient became edematous. When regular dilatations were begun again, a No. 14 F bougie was passed with some difficulty.

After two weeks the diarrhea subsided completely. Since then the child has gained weight progressively. Dilatations have been continued once or twice weekly, and at the present time the patient weighs 18 pounds. He appears to be developing normally and is taking all of his feedings by mouth. A No. 30 F bougie is being passed through the esophagus at intervals of one week. Roentgenologic examination reveals a narrowing at the site of the anastomosis, but there is no delay of thin barium feedings at the site of the stricture.

**DISCUSSION OF CASES**—In attempting to evaluate the cases which have been operated upon, several factors are apparent. In the first case observed, a tight-fitting mask and positive pressure anesthesia were employed. During the course of the operative procedure the stomach became greatly distended with gas. It should be realized that this is bound to occur, since the stomach communicates with the trachea. The same thing occurred at the time of the second operation upon Case 4. In this case the esophagus had been ligated with umbilical tape at the esophageal hiatus of the diaphragm through an abdominal incision. Twenty-five days afterward the infant coughed up a small amount of the feeding which had been given through the gastrostomy tube. At operation, and later at autopsy, it was proven that the esophagus had recanalized. The tape ligature was found lying within the lumen of the cardiac end of the stomach at autopsy.

Thus, a transpleural incision is not desirable if one expects to resort to the use of the tightly-fitting mask and positive pressure anesthesia. Furthermore, simple ligation of the lower segment of the esophagus, particularly at its lower end, is likely to be followed by recanalization of the esophagus two or three weeks later.

A posterior retropleural incision was employed in five of these cases. In four of these the incision was made on the right side, the azygos vein being



doubly ligated and divided. We feel that this is preferable to an incision on the left side, where the arch of the aorta lies in the way. The one successful operation reported here was accomplished through an incision made on the left side, however.

The position of the fistula between the lower segment and the trachea is variable. In two of the cases reported here the fistula was directly at the carina. In the remaining cases the fistula was in the posterior wall of the trachea, somewhat above the bifurcation. The length of the upper segment varies also. In Case 7, the upper segment was unusually short, and tension on the suture line was extreme. Exteriorization of the upper segment and gastrostomy should have been resorted to in this case when it became apparent that the anastomosis could not be satisfactorily accomplished. The distance between the two segments in Case 6 was all of two centimeters. The upper segment was fairly long and although the fistula was at the carina and the upper end of the lower segment was extremely small, it was possible to "telescope" it into the upper segment because of the mobility of the upper segment and the slight upward displacement of the lower segment which was effected by means of traction on the catheter.

In Case 5 the operative procedure was too great. Cervical esophagostomy and gastrostomy should have been deferred and performed at another time.

COMMENT. There have been approximately 400 cases of this type of congenital abnormality reported. The condition is undoubtedly more common than this number would seem to indicate.

There have been two methods of approach to the surgical treatment of this condition. The first aims to interrupt the continuity of the lower segment of the esophagus and to create an esophagostomy by bringing the upper segment to the skin of the neck. The construction of a subcutaneous epithelial-lined tube to communicate between the upper segment of the esophagus and the stomach is undertaken later. Such a plan obviously requires several operations. The second plan is directed toward the establishment of continuity of the esophagus within the thorax. The latter plan, accomplished in a single operation, is the ideal one.

Leven,<sup>3</sup> in 1941, reported the first successful operation for congenital esophageal atresia, with tracheo-esophageal fistula. This child was operated upon in November, 1939, and is still alive. A gastrostomy was first performed, followed at successive operations by extrapleural ligation of the fistula and cervical esophagostomy. An external esophagus has since been constructed. Since that time several additional successful procedures of this type have been reported (Ladd, Humphreys, Haight).

In June, 1943, Haight and Towsley<sup>4</sup> reported the first successful operation for the establishment of the continuity of the esophagus. Since then, seven additional successful operations have been reported, five by Haight,<sup>5</sup> one by Humphreys,<sup>6</sup> and one by Ladd.<sup>7</sup>

It is our belief that the fistula should be exposed at operation in all cases and that it should be closed and the lower segment of the esophagus divided

as near the fistula as possible. In the seven cases reported here, the fistula has been exposed at the first operation upon six patients, and ligation and division of the lower segment was performed in five.

Following closure of the fistula an attempt should be made to effect an anastomosis of the two segments of the esophagus. The upper segment lies very high in the thorax, and its length is variable in different infants. It may be exposed by dissecting just behind the trachea. It is usually easily recognizable. Its position is not fixed, as is the end of the lower segment, but it moves up and down with movements of the child.

If the distance between the two segments is so great, or the lower segment is so delicate, that a direct anastomosis cannot be accomplished, the wound may be closed and the infant turned on his back, where a short incision may be made along the anterior border of the lower end of the left sternocleidomastoid muscle. The upper segment can be easily located, freed, and brought out to the skin. It should be pointed out that the operation performed upon the one successful case in this series was upon an infant in whom the lower segment communicated with the trachea at the carina and that the upper end of the lower segment was very poorly developed, being composed on its anterior side of only the mucous membrane. A procedure such as the one employed here may be useful in the construction of an intra-thoracic esophagus even when there is a considerable defect in the continuity of the esophagus and where the lower segment is so poorly developed as to make end-to-end suture, without the aid of a catheter, or some similar device, impossible.

Thus, by directly attacking the fistula, one may accomplish end-to-end suture in a fair number of patients, and if it is obvious at operation that this cannot be done, the upper segment may still be exteriorized. Gastrostomy should then be performed. If the infant's condition is poor, the last two procedures should be deferred until later.

#### SUMMARY

Seven infants have been operated upon in the Vanderbilt University Hospital for congenital atresia of the esophagus during the last three years. The author's experience in the management of these patients is reviewed. In one case a successful end-to-end anastomosis of the esophageal segments was performed. This child is living, and is in good condition. This case is reviewed in detail.

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# VARICOSE VEINS

## ANATOMIC FINDINGS AND AN OPERATIVE PROCEDURE BASED UPON THEM

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THE PUBLISHED RESULTS of the therapy of varicose veins and post-thrombophlebitic processes in the thigh and leg still leave much to be desired. Though high ligation offers many advantages over older methods of treatment, too often (as pointed out by Harkins,<sup>1</sup> Ochsner and Mahorner,<sup>2</sup> and others), the desired improvement is not achieved because other sites in the lower limb possess incompetent or potentially incompetent perforator veins not controlled by the operative procedure. Our own study of 214 patients who had had high ligation combined with retrograde injections of sclerosing solution showed that, in 46 per cent, the result was not wholly satisfactory (Table I), some even requiring further operative procedures.

TABLE I  
RESULTS\* IN 214 PATIENTS (372 LOWER LIMBS) TREATED BY HIGH LIGATION AND  
RETROGRADE INJECTION OF SCLEROSING SOLUTION

	No	Per Cent
Faulty high ligations	19	5
<i>Improvement — Objective</i>		
Reflux flow of blood 16-40 seconds†	201	54
Reflux flow of blood 0-15 seconds†	171	46
<i>Improvement — Subjective</i>		
75-100%†	189	51
50- 75%†	82	22
Less than 50%†	101	27

\* Average length of time since operation 3 years 8 months

† Multiple tourniquet tests were employed and observations taken with the tourniquet applied at the groin in order to rule out inaccuracy of the high ligation procedure

Of the various tests designed to locate the incompetent perforator veins contributing to the poor results mentioned, probably the most important is the multiple tourniquet test. This yields valuable information but is not sufficiently precise to disclose the exact location of the incompetent perforator veins.

The evident failure of therapy in a considerable number of cases and the inadequacy of the tests for the location of incompetent perforator veins in the thigh led to anatomic studies on the cadaver. In a preliminary report<sup>3</sup> the results of dissections on 19 cadavers (36 thighs), and 43 surgical dissections were outlined. Since that time, anatomic dissections have been carried out on 54 additional cadavers (101 thighs) and 703 surgical dissections have been made. These not only have confirmed the studies previously reported but have yielded additional anatomic data which form the basis of a surgical procedure giving promise of materially improving the therapy of varicose veins by aiding in the elimination of incompetent or potentially incompetent perforator veins of the thigh.

It is the purpose of this paper to present the results of these anatomic studies and describe the operative procedure to which they contributed

#### ANATOMIC STUDIES

The location and number of perforator veins connecting the saphenous system with the deep veins of the thigh vary greatly. Nevertheless, certain generalizations can be made. For instance, the long saphenous vein consistently joins the femoral vein in the inguinal region. Despite many variations, the superficial epigastric, superficial iliac and superficial pudendal veins are always represented in some manner. Dissections of the thigh disclosed the fact that, although variations are numerous, there is a scheme of placement of the long saphenous vein and the perforator veins of the thigh, so that there may be said to be a general pattern (Fig 1, Type I) with three main variations in type (Types II, III and IV) described below.

The embryonic pattern of the saphenous system (Type I, Fig 1) consists of two saphenous stems in the thigh. The main long saphenous vein (B) is usually larger, deeper and more medial than the accessory vein (A). In the upper part of the thigh both tributaries of the long saphenous vein (A, B) are found in the expected location, superficial to the deep fascia. At a varying level (C) in the upper half of the thigh, however, one tributary (B') of the main long saphenous vein B pierces the superficial layer of the deep fascia, thereafter coursing deep to the deep fascia, whereas the accessory saphenous vein A remains superficial to the deep fascia throughout its entire course. This tributary (B') which courses beneath the superficial layer of the deep fascia, assumes great importance because from it arise the main perforator tributaries which connect it with the femoral and popliteal veins of the thigh (Fig 1, H, J, K), discussed later. After coursing down the thigh for six centimeters, or more, this deep saphenous tributary again divides. One tributary (B'') emerges from beneath the deep fascial layer at D to reoccupy a position superficial to the deep fascia and the other (B''') continues down the thigh and leg between deep fascial layers.

Type II (Fig 2) varies from Type I in the absence of the accessory saphenous vein A. Type III (Fig 3) varies from Type I in that the accessory saphenous vein A, although present, does not connect with the femoral vein near the saphenous-femoral junction, but does connect with the main saphenous vein at C just above the site where the main saphenous vein dips beneath the deep fascia. Type IV (Fig 4) is like Type I except for an apparent lack of connection at C between the lower end of the accessory saphenous vein A and the main saphenous vein B. The saphenous vein, or any of its divisions or tributaries, may be double or even triple, and considerable variation may exist in the manner in which the perforator tributaries of vein B' connect with the deep circulation.

#### MID-HUNTER CANAL PERFORATOR VEIN

Along with the observations made on the saphenous vein and its subdivisions, described above, it was noted first in anatomic then in surgical

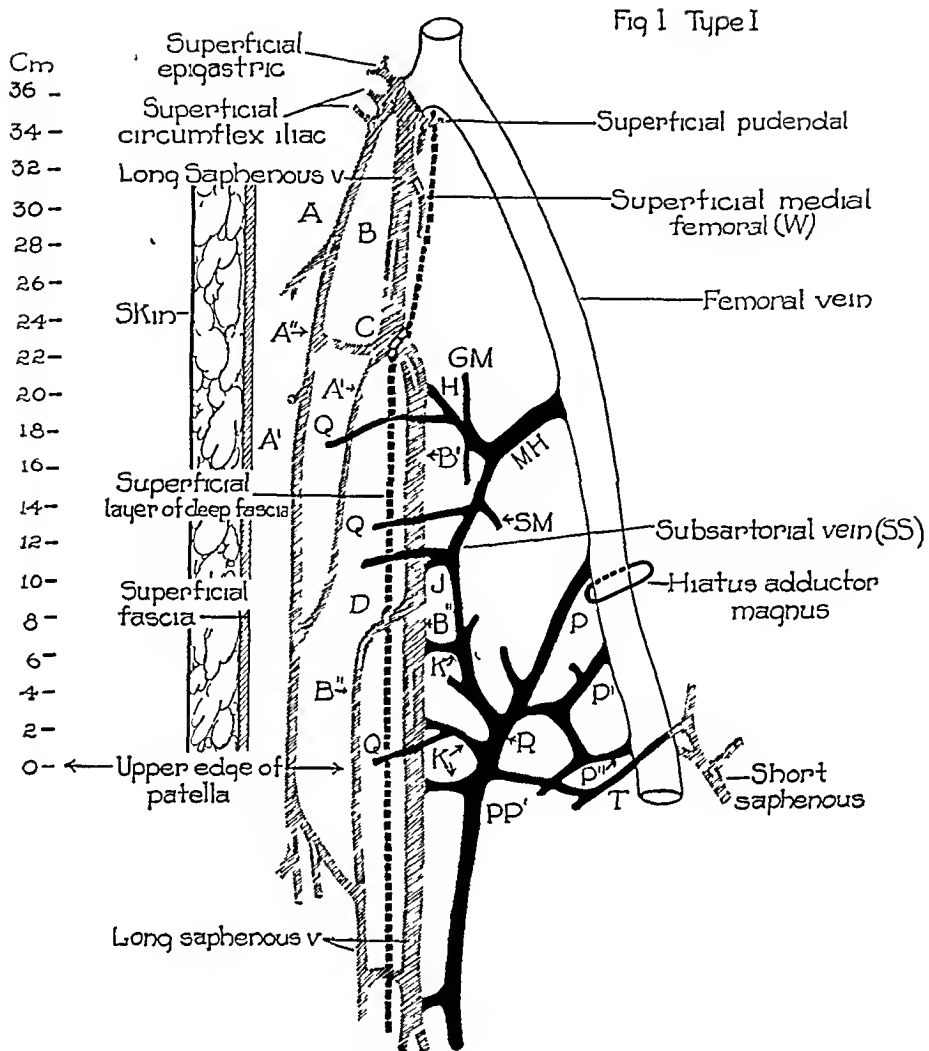


FIG 1.—Drawing showing the saphenous system as A, A', A'', and B, B', B'', B''' Veins A, A', A'', B lie superficial to the deep fascia, whereas distal to C, veins B', B'', B''' lie beneath the superficial layer of the deep fascia. Vein B''' emerges from beneath the deep fascia at D. Perforator vein H connects the main saphenous vein B' with the constant mid Hunter canal perforator vein MH.

The genicular venous plexus is composed of the highest genicular vein, P, superior medial genicular vein, P', inferior medial genicular vein, P'', and a tributary, T, of the short saphenous vein. A tributary, PP', of the deep saphenous drains the medial aspect of the leg and empties into the genicular plexus.

The subsartorial vein connects the mid Hunter canal vein with the genicular plexus at R.

Accessory perforator veins, Q, emerge into the superficial fascia without making direct connections with the main saphenous stem B' B''. Perforator veins J, K make direct connections between the main saphenous stem B' and the subsartorial vein.

SM and GM are tributaries draining the sartorius and gracilis muscles.

dissections, that at a point in the thigh varying from 16 to 22 cm above the upper edge of the patella, lies a constant tributary (MH) of the femoral vein. This tributary, accompanied by a branch of the femoral artery and one of the saphenous nerve, pierces the deeper fascial layers to become more superficial than the femoral vein. It divides into several tributaries which drain adjacent muscles, especially the gracilis (GM) and sartorius (SM). Of utmost importance is the fact that, with great constancy, *at least one of these tributaries of vein MH connects with the deep saphenous vein (B')* in the midthigh. Because this perforator vein (MH, H, Fig 2) connects

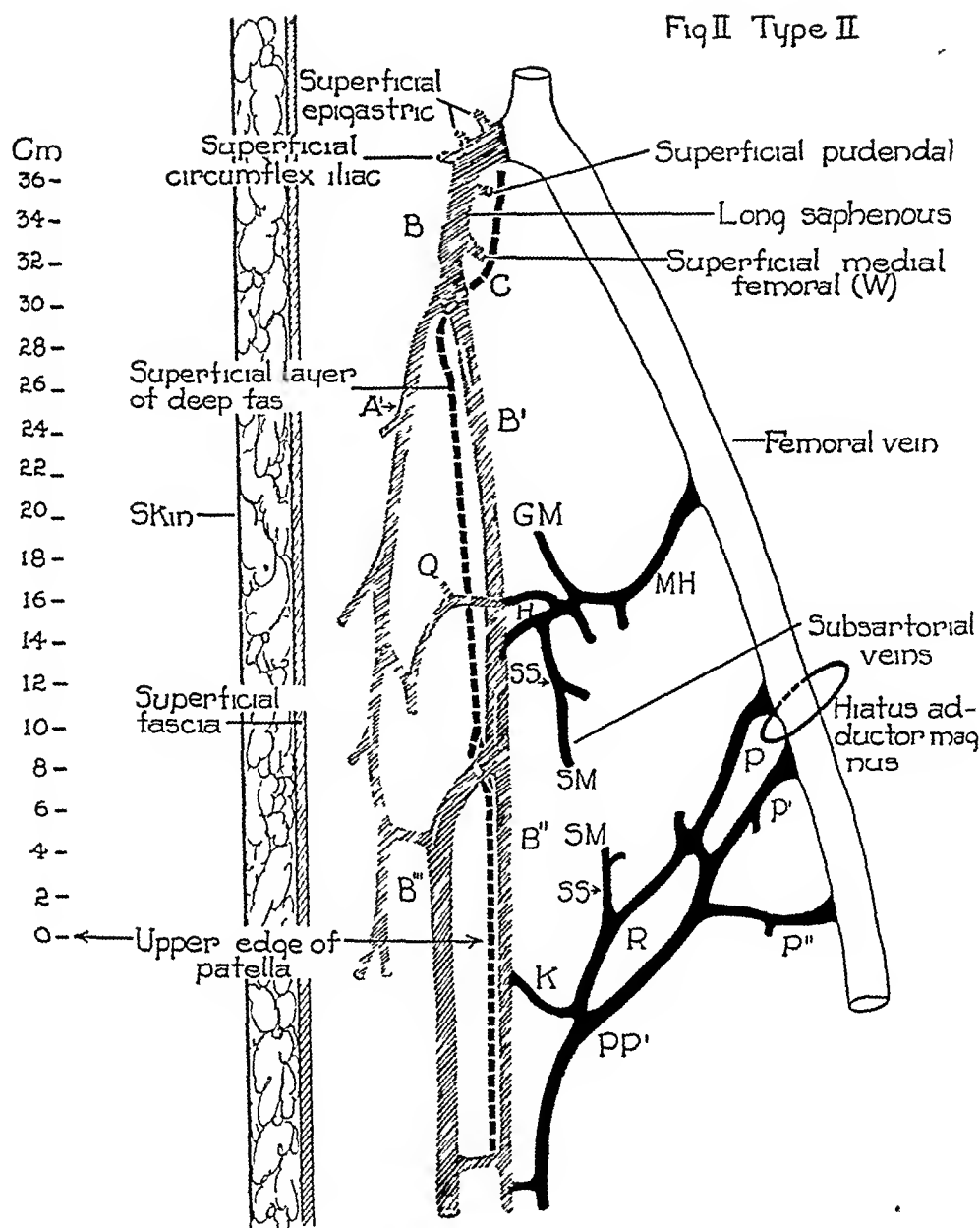


FIG 2—Drawing showing the saphenous system as B, B', B'', B''', A' (Note that the saphenous system in the upper thigh consists of a single stem, B) Veins B, A', B' lie superficial to the deep fascia, whereas distal to C, Veins B', B'' lie beneath the superficial layer of the deep fascia

Perforator vein H connects the main saphenous vein B' with the constant mid Hunter canal perforator vein MH

The genicular venous plexus is composed of the highest genicular vein, P, superior medial genicular P', inferior medial genicular vein P'' A tributary, PP', of the deep saphenous drains the medial aspect of the leg and empties into the genicular plexus

The subsartorial vein (SS) consists of a proximal segment which drains into the mid Hunter canal plexus and a distal segment which drains into the genicular plexus at R

Accessory perforator vein Q emerges into the superficial fascia without making direct connection with the main saphenous stem B' Perforator vein K makes direct connection between the main saphenous stem B'' and the genicular plexus

SM and GM are tributaries draining the sartorius and gracilis muscles

with the femoral vein at about the middle of Hunter's canal it has been designated as the mid-Hunter canal perforator vein In a total of 56 consecutive anatomic examinations, this vein was found in each

Another constant tributary of the mid-Hunter canal vein (MH) is one that drains the sartorius muscle This tributary (SS) has been given the name of subsartorial vein After coursing distally for a few centimeters, it most often terminates within the sartorius muscle (Fig 2) but in a con-

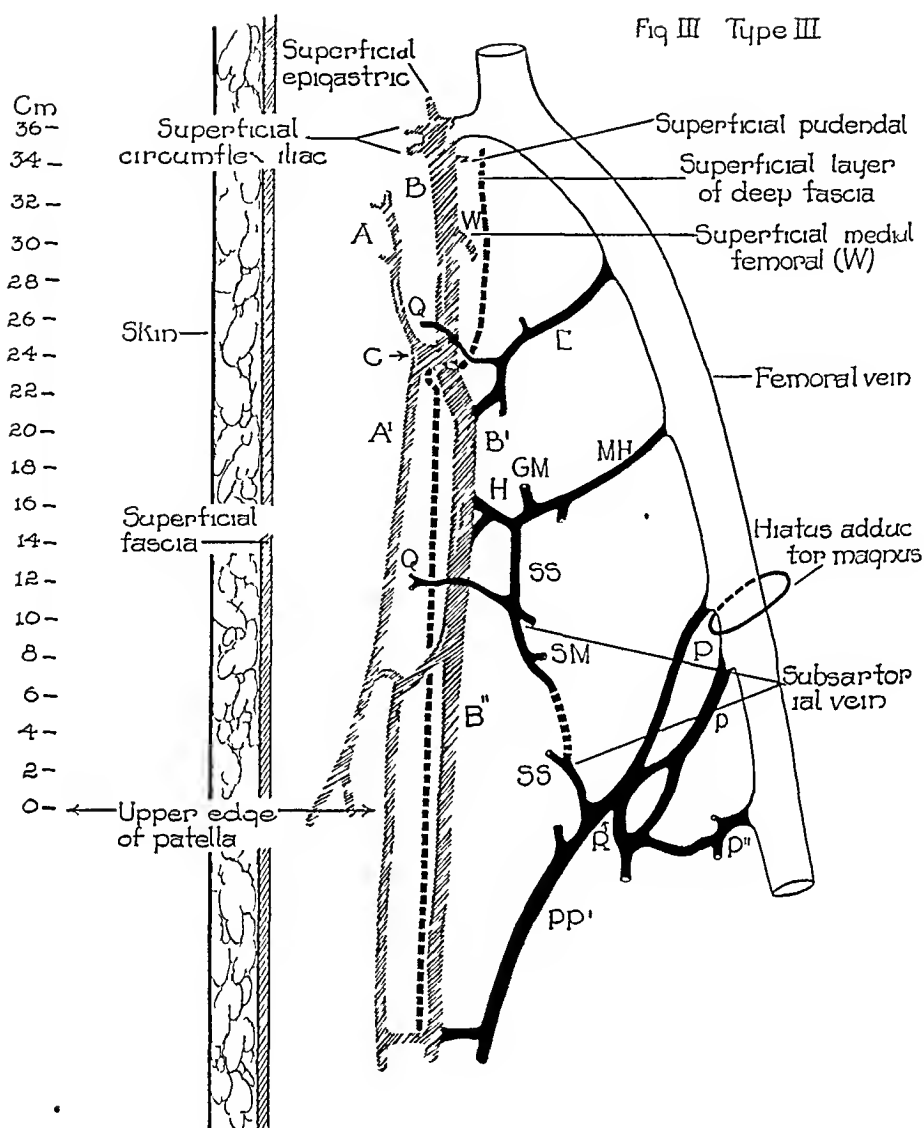


FIG 3—Drawing showing the saphenous system as A, A', B, B', B''. Note that vein A connects with the main saphenous stem B at point C but makes no apparent connection with the proximal end of vein B. Veins A, A', B lie superficial to the deep fascia, whereas distal to C, veins B', B'' lie beneath the superficial layer of the deep fascia.

A high Hunter canal perforator vein, E, occasionally connects the proximal portion of vein B' with the femoral vein. Perforator vein H connects the main saphenous vein B' with the constant mid Hunter canal perforator vein MH.

The genicular venous plexus is composed of the highest genicular vein P, superior medial genicular vein, P', inferior medial genicular vein, P''. A tributary, PP', of the deep saphenous drains the medial aspect of the leg and empties into the genicular plexus.

The subsartorial vein SS makes connections within the sartorius muscle between the mid Hunter canal vein and the genicular plexus at R. Accessory perforator veins Q, emerge into the superficial fascia without making direct connections with the main saphenous stem B'.

SM and GM are tributaries draining the sartorius and gracilis muscles.

sideable number of cadavers it was found not only to drain this muscle but to continue distally to connect with the vein PP' at R (Fig 1). The importance of this subsartorial vein lies in the fact that from it often arise perforator tributaries which connect with the deep saphenous vein B' or B''. It is interesting to note that, whenever the upper subsartorial vein ends within the sartorius muscle, a tributary of the vein PP', arising at R, travels

# VARICOSE VEINS

Fig IV Type IV

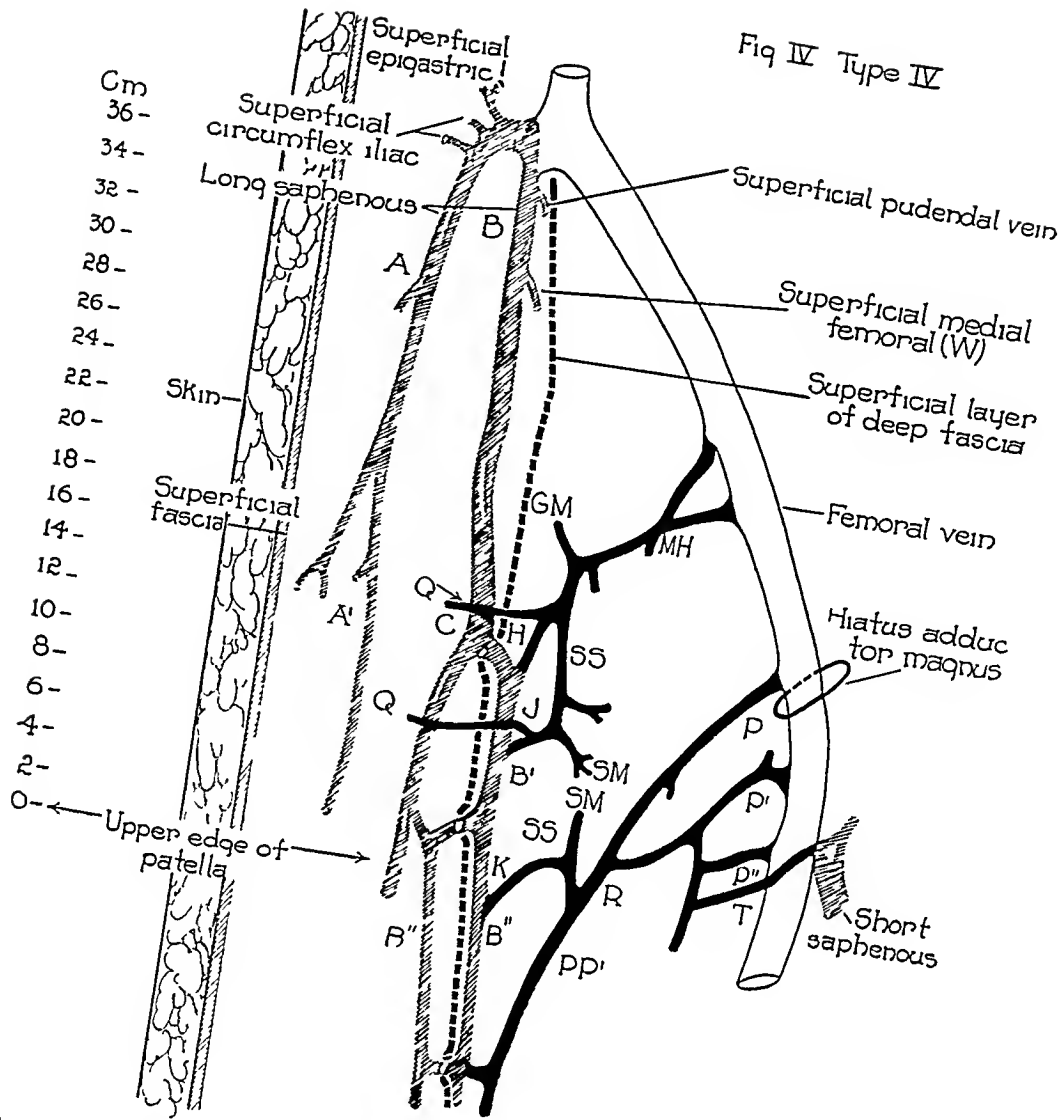


Fig 4—Drawing showing the saphenous system as A, A', B, B', B'',. Note that vein A, A', makes no apparent connection with vein B at C. Veins A, A', B lie superficial to the deep fascia, whereas distal to C, veins B', B'' lie beneath the superficial layer of the deep fascia.

Perforator vein H connects the main saphenous vein B' with the constant mid Hunter canal perforator vein MH.

The genicular venous plexus is composed of the highest genicular vein, P, superior medial genicular vein P', inferior medial genicular vein P'' and a tributary, T, of the short saphenous vein A tributary, PP', of the deep saphenous drains the medial aspect of the leg and empties into the genicular plexus.

The subsartorial vein, SS, consists of a proximal segment which drains into the mid Hunter canal venous plexus and a distal segment which drains into the genicular plexus at R.

Accessory perforator veins, Q, emerge into the superficial fascia without making direct connections with the main saphenous stem B'B''. Perforator veins J, K make direct connections with the main saphenous stem B'B'' and the subsartorial vein SS.

SM and GM are tributaries draining the sartorius and gracilis muscles proximally to enter the sartorius muscle (Figs 2 and 4) and sometimes connects with the upper subsartorial vein within the sartorius muscle (Fig 3). Again, even though the lower subsartorial vein apparently has no direct connection with the upper subsartorial vein, it also may possess perforator tributaries (K) which connect with saphenous vein B'' (Fig 4).

In four cadavers and twelve surgical dissections a relatively rare tributary (E, Fig 3) was found. This particular vein, aside from furnishing



tributaries to adjacent muscles, connects the upper part of the deep saphenous vein B' with the femoral vein at a point from six to eight centimeters below the sapheno-femoral junction. This vein may possibly be a constant tributary of the femoral vein, but because connections between it and the saphenous vein B' are rare, no detailed studies have as yet been attempted. In future dissections, however, this vein will be investigated more thoroughly.

#### GENICULAR VEIN PLEXUS

The area superficial and deep to the deep fascia of the upper and medial aspects of the leg is drained by a tributary PP' of the saphenous vein. This tributary extends proximally beneath the insertion of the sartorius muscle, passes between the sartorius and gracilis muscles, and lies beneath the deep fascial layer at the lower level of the knee. It anastomoses with the inferior (P'') and superior (P') medial genicular veins below the hiatus of the adductor magnus muscle. Also, it often possesses a connection with a tributary (T, Fig 4) of the short saphenous vein. This saphenous tributary (PP') then courses upward to become the highest genicular vein (P) which pierces the aponeurotic covering of the adductor canal and connects with the femoral vein immediately above the hiatus of the adductor magnus muscle. The saphenous nerve accompanies this saphenous tributary of the highest genicular vein. The importance of the saphenous tributary PP' lies in the fact that veins often connect it with the deeper saphenous vein B'' by tributaries (K). Moreover, as previously mentioned, this vein PP' occasionally connects with the subsartorial vein at R (Fig 1). Of utmost importance is the fact that from the tributary veins MH, H, SS, J and K often arise one or more tributaries which extend independently into the superficial tissues, having no connection with the main saphenous vein. These veins (Q, Fig 4) have been designated as accessory perforator veins.

Figures 1, 2, 3 and 4 are composite illustrations abstracted from studies on the cadaver and are designed to indicate the most important variations in the placement of the veins of the medial portion of the thigh.

It is to be noted that the constant veins B', B'', H, MH, SS, PP', P and P' are present in all four types. Also the inconstant veins, J, K, E and Q may be present in any of these types. Again, although in all types the vein B usually pierces the superficial layer of the deep fascia at about the junction of the upper with the middle third of the thigh, there may be some variation in this arrangement and to emphasize such variation, vein B is depicted in Figure 2 as piercing the fascia high in the thigh, while other possible sites are indicated in Figures 1, 3, and 4. The distribution of veins by type in the cadaver and in surgical dissections is shown in Table II. Table III shows measurements taken from dissections on the cadaver.

Figures 1 to 4 show main groups of perforator veins on the medial aspect of the thigh, namely those of (a) the sapheno-femoral junction, (b) the mid-Hunter canal vein, and (c) the genicular plexus. In the literature upon this subject, it has been stated that there are from one to seven perforator

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TABLE II  
CLASSIFICATION ACCORDING TO TYPES OF VEINS IN THIGH  
Dissections†

	Anatomic		Surgical	
	No	Per Cent	No	Per Cent
Type I	9	8.91	43	7.5
Type II	62	61.38	365	64.0
Type III	3	2.97	14	2.5
Type IV	27	26.74	149	26.0
Total typed	101		571†	

\* A total of 137 anatomic and 703 surgical dissections (465 patients) formed the series of which 101 and 571, respectively, were typed

† The cases before 1942 were not classified, as a sufficiently definite pattern had not been established

TABLE III  
MEASUREMENTS† NOTED IN ANATOMIC DISSECTIONS

	Greatest Length Cm	Shortest Length Cm	Average Length Cm	No of Dissections
Sapheno-femoral junction	37.00	32.00	35.25	137
Point C (Fig. I)	33.00	13.50	20.37	101
Junction mid-Hunter perforator with saphenous	20.30	11.10	15.60	67
Junction mid-Hunter perforator with femoral	23.00	15.00	18.50	56
Junction highest genicular with femoral	13.00	9.00	10.60	34

† All measurements were taken from the upper edge of the patella.

veins connecting with the long saphenous vein. In 101 anatomic dissections the largest number found was six, the smallest, one, the average number being 1.94. All these perforator veins were found to arise from the mid-Hunter canal vein, the genicular plexus or the subsartorial vein which connects them.

Further anatomic studies on the veins of the thigh demonstrated that many other perforator veins exist, but with the exception of three main sites, discussed under operative treatment, they pierce muscles, and the protection afforded by these muscles seems to preclude the possibility that these veins will become incompetent.

Six principal findings resulted from the anatomic dissections described above: (1) The recognition of a pattern in the placement of the long saphenous vein and its tributaries, with the occurrence of four anatomic types. (2) The fact that the main stem (B) of the long saphenous vein lies deep to the deep fascia somewhere along its course (B', B'') rather than remaining superficial to the deep fascia. (3) A constant tributary (MH) of the femoral vein, named the "mid-Hunter canal perforator vein" by reason of its position, connects by one or more tributaries with the long saphenous vein as it courses beneath the deep fascia. (4) The genicular vein plexus is constant. (5) The subsartorial vein occasionally connects the mid-Hunter canal vein with the genicular system. (6) The so-called perforator veins on the medial aspect of the thigh arise mainly from the sapheno-femoral junction, the mid-Hunter canal vein, the genicular plexus, and the subsartorial vein.

## SURGICAL APPLICATION

The treatment of incompetent or potentially incompetent perforator veins in the thigh depends upon a full realization of the importance of the pattern described under anatomic findings and especially of the rôles played by the deep saphenous tributary B', the mid-Hunter canal perforator system and the genicular plexus. Eradication of the deep long saphenous stems B' and B'' disconnects the direct communication of the saphenous vein with the femoral or popliteal veins, but does not eliminate the indirect accessory perforator (Q) veins. To efface all incompetent or potentially incompetent perforator veins of the medial thigh requires, in addition, transection of the mid-Hunter canal vein (MH) near the femoral vein, transection of the vein PP' deep to the point R and excision of certain parts of the subsartorial vein. This should prevent the reflux flow of blood from the deep veins of the thigh by severing those incompetent veins which communicate between the deep and superficial systems.

The surgical procedure based upon the information gained from the anatomic studies described is one which, in our hands, has materially improved the results of the therapy of varicose veins. Furthermore, it involves a minimal amount of trauma and has the advantage of keeping patients in bed for very short periods of time. It consists of a combination of injection of veins, high ligation of the saphenous vein, elimination of the main saphenous stem (B', B''), eradication of the mid-Hunter canal vein and, in certain cases, excision of the high-Hunter canal vein (Fig 5) and elimination of as much of the genicular venous plexus as may seem to be required. The basically new approach is the employment of sclerosing solution as an agent for suppression of hemorrhage so that the surgical procedure can be performed without danger of postoperative bleeding. Patients can be out of bed and active within 24 hours after operation. The early activity combined with firm thrombosis of the cut veins also reduces the danger of pulmonary infarcts by emboli.<sup>4</sup>

## OPERATIVE PROCEDURE

Varices below the knee are thoroughly sclerosed by local injection previous to operation. Under local or spinal analgesia, sodium pentothal or other general anesthesia, the sapheno-femoral junction is exposed through a longitudinal incision. After identification of the saphenous vein, a clamp is applied to stem B of this vein and a retrograde injection of about four cubic centimeters of a sclerosing solution is used. An interval of from 10 to 15 minutes is then allowed to elapse during which time the upper ends of the long saphenous vein or veins are dissected and their upper tributaries exposed, ligated and divided. The procedure of the high ligation<sup>5, 6</sup> is now so fully standardized that further comment on this aspect of the operation is unnecessary. In the majority of patients with double long saphenous veins, most of the tributaries at the upper end of the saphenous system arise from vein A. A ligation performed as indicated by M (Fig 5) would

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Fig V

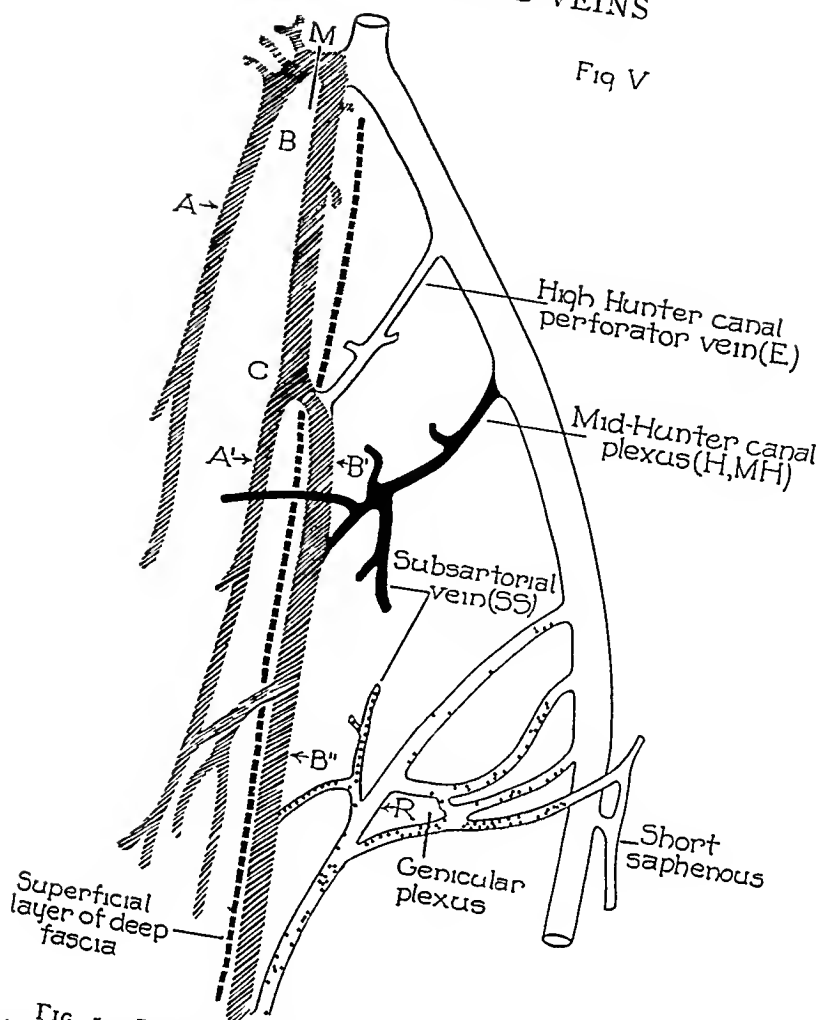


FIG 5—Drawing showing the saphenous system as A, A', B, B', B''. Veins A, A', B, distal to C, veins B', B'' lie superficial to the deep fascia, whereas R designates the point at which the subsartorial vein connects with the genicular plexus. Line M illustrates the danger of mistaking superficial vein A for the main saphenous vein, in patients who possess double long saphenous veins.

leave vein B patent and the operative procedure would fail to accomplish its purpose.

At the end of 10 or 15 minutes it will be found that the sclerosing solution has caused a thrombosis in the affected vessels which usually will prevent bleeding when the veins are transected. It is important however to test the effectiveness of the sclerosis by momentarily releasing the clamp and observing that no fresh blood flows from the open end of the vein. If bleeding should occur, as rarely it does, more sclerosing solution should be injected. If there is doubt that the sclerosing solution has effectually suppressed all hemorrhage, the tributaries of the offending vessel should be ligated, or if the bleeding cannot be exactly located, firm bandaging of the limb will control it.

The next step is the elimination of the perforator veins of the thigh. Although the point at which the main saphenous vein dips beneath the superficial layer of the deep fascia is usually located at about the junction of the upper and middle thirds of the thigh, its exact position is variable.

After transecting the nearly constant superficial medial femoral vein which lies in the superficial fascia on the inner aspect of the upper eighth of the thigh, a Mayo stripper may be placed outside the main saphenous vein and the vein stripped distally until rather marked resistance is encountered, which is usually at or about point C. When this is located, a longitudinal incision about eight centimeters in length is made over, and parallel with, the saphenous vein just distal to the point of resistance. Vein B' is identified and tributary A' is separated from the main saphenous vein B, B'. Once the vein B' is identified it is simple to ascertain that it pierces the fascia and, by making traction on the excised vein B, the vein B' can be felt beneath the superficial layer of the deep fascia. This deep fascia is longitudinally incised, the vein B' is separated from the tissues superficial to it, great care being taken not to disturb the tissues beneath the vein. A large self-retaining thyroid retractor is placed in the wound. Vein B is grasped with a clamp and by distal retraction of vein B' its undersurface is carefully dissected free. Constant search is maintained for the high-Hunter canal perforator vein and the mid-Hunter canal vein. Whenever the inconstant high-Hunter canal vein is found, it is dissected to its junction with the femoral vein, where it is ligated and excised. The mid-Hunter canal vein, which is usually present, varies greatly in size and length and much diligence may be required to locate it. When discovered it can be grasped with a hemostat and separated from the saphenous vein. The mid-Hunter canal vein is dissected to its approximate junction with the femoral vein where it is ligated and transected. The femoral vein is not usually identified as such, the approximate junction of the mid-Hunter canal vein with the femoral vein being ascertained by feeling the pulse of the femoral artery. The subsartorial vein and the deeper portion of the mid-Hunter canal vein are usually exposed simultaneously. The subsartorial vein should be followed distally as far as is practical, usually from five to seven centimeters, transected and ligated.

Although the sclerosing solution usually controls any bleeding from the subsartorial vein, its efficacy in such control of the proximal end of the cut mid-Hunter canal vein cannot be relied upon, hence the necessity of ligation.

Upon completion of the eradication of the mid-Hunter canal perforator system, the vein B' is again picked up with a hemostat, and if any portion of this incision remains unexplored, dissection of the vein B', B'' is carried further caudal, a search being made for any perforating vein that might possibly be present.

If the multiple tourniquet test previously performed indicated no incompetent perforator veins in the lower fourth of the thigh, a Mayo stripper can be applied to the vein B', B'', and it can be excised by stripping. If, however, previous tests have disclosed the presence of incompetent perforator veins in the vicinity of the adductor tubercle, they must be searched for and eradicated. A longitudinal incision about eight centimeters in length is made over the deep saphenous vein B'' in the vicinity of the adductor tubercle, and this vein is exposed by incising the super-

ficial layer of the deep fascia over it. A search for a perforator vein is instituted in a manner similar to that described in locating the mid-Hunter canal in the midthigh. Once identified, the perforator vein should be followed deeply until point R is exposed. The highest genicular vein, the superior and inferior medial genicular veins of the genicular plexus, and, if present, any tributary making connections with the short saphenous vein, are then followed deeply and ligated near their junctions with the femoral, popliteal, or short saphenous veins.

The next step consists of elimination of varices and incompetent perforator veins in the leg. If the preliminary examination of the patient disclosed no incompetencies of the perforator veins below the knee, varices are removed wherever present. If, however, the multiple tourniquet test demonstrated deficiencies of the perforator veins in this area, the treatment is more complicated. Linton<sup>7</sup> and Warwick<sup>8</sup> pointed out that the perforating veins of the medial aspect of the leg usually make direct and nearly horizontal communications between the deep veins and the saphenous system. For this reason the multiple tourniquet test is valuable in locating the sites of incompetent perforator veins of the leg. Although we have made no exhaustive studies on the leg of the cadaver, surgical dissections have indicated three important locations for deficient perforator veins on the medial aspect of the leg. In order of their frequency they are: 1. From 18 to 22 cm. above the sole of the foot. 2. At about the junction of the upper and lower half of the leg (Medial margin of the tibia). 3. At about the middle of the proximal third of the leg. When indicated, these incompetent perforator veins are followed to a point beneath the deep fascia where they are ligated and excised. The rent in the fascial layer is obliterated by appropriate sutures. Whenever the short saphenous vein is found to be incompetent it is ligated and transected at its junction with the popliteal vein. All tributaries within approximately six centimeters of this junction are also ligated. If incompetent perforator veins are found on the lateral aspect of the thigh, they are followed to a point three or four centimeters beneath the deep fascia, within the intramuscular septa, where they are ligated and excised.

**DISCUSSION**—Patients who have had one lower limb treated by means of the combined high ligation operative procedure and retrograde injections of sclerosing solution, and the companion extremity treated in the manner described in this paper, observe that the postoperative discomfort is much less noticeable in the latter procedure. This lessening of pain probably results, at least partly, from the fact that the veins, although exposed to the action of the sclerosing solution, are removed and, thus, the usual inflammatory reaction from the injection is avoided.

In the removal of veins so treated, some of the sclerosing solution may remain in the wound, though every effort is made to remove it. In no case did it cause any evident damage. Substantiating this view is the fact that synasol, an excellent chemical for sclerosing veins, has also been in-

jected into tissues for treating inguinal hernia without causing appreciable damage to tissue. Indeed, sylvasol is not very different chemically from any other sclerosing soap. In patients who exhibited sensitivity to monolate or similar compounds, the necessary use of quinine hydrochloride and urethane or sugar solutions caused no obvious difficulty.

Insufficient time has elapsed for proper evaluation of the late effects of this procedure. It would appear, however, that the method should reduce the incidence of recurrence. In the entire group of 465 patients, no deaths, massive hematomata or pulmonary embolisms occurred. There were ten mild infections, one rather severe infection and two traumatic cysts. Of these infections only two involved the thigh. The average time of hospitalization was 28 days. All patients were walking within 28 hours after operation.

#### SUMMARY

1 A general scheme of arrangement of the saphenous system in the thigh exists but variations are common.

2 The occurrence of a heretofore unrecognized location of the saphenous vein between the deep fascial layers, of a constant mid-Hunter canal perforating vein at about the junction of the upper and middle thirds of the thigh, and of an inconstant perforator vein connecting with the medial genicular venous plexus and the subsartorial vein is described.

3 Although anatomic variations are common, a definite plan exists, the surgical significance of which is emphasized.

4 Suggestions are made for what appears to be a more effective operative therapy.

Acknowledgment is made to Dr. John B. deC. M. Saunders, Professor of Anatomy at the University of California, for his assistance in confirming the anatomic findings presented in this article.

Acknowledgment also is made to Lt. Comdr. K. A. Tuttle for the financial assistance which made this research possible.

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# AN IMPROVED METHOD FOR COLLECTING, CENTRIFUGING AND POOLING BLOOD PLASMA

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CURRENT experimental and clinical publications reveal increasing interest in preserved blood plasma in various forms. The present communication is concerned with the description of a closed method for collecting, centrifuging and pooling blood plasma. Of 23 different types of containers which we devised and tried, the one described here was found most satisfactory.

*Description of Container* —We have designed a pyrex glass container which has a capacity of 300 cubic centimeters (Fig 1A). The bottom, which is rounded off, leads into a narrowly constricted portion having an inside diameter of three millimeters. Below this constriction is a small bulb with a capacity of approximately two cubic centimeters. Below this is a similar second bulb with a small hole through which a needle can be inserted for drawing off the cells from the bottom of the container. At the upper end is a constricted portion, or neck, one centimeter in diameter.

*Procedure* —Before use, the container and all other material are cleansed well by means of soap and water, cleaning solution and distilled water. A piece of rubber tubing, (size  $\frac{3}{16} \times \frac{1}{16}$  inch) one inch (2.5 cm) long is then drawn over the lower bulb to seal the small hole where the cells are to be drawn off. A vaccine cap is placed over the neck of the container. An air vent (Fig 2A) is then inserted through the vaccine cap to allow the air within the container to escape while it is being filled with blood. The air vents are made by cutting a glass needle adaptor in half, filling it with cotton and attaching a No. 15 needle (Fig 2A). A piece of rubber intravenous tubing (Fig 2B) approximately 15 inches (37.5 cm) long is then drawn over a No. 15 needle at one end. The other end is fitted over a glass needle adaptor which holds a No. 15 intravenous needle. The end without an adaptor is inserted through the vaccine cap, beside the air vent. The entire set-up is then wrapped and sterilized all assembled.

To collect the blood the patient is placed on the table and the arm prepared and draped in the usual manner. Forty-five cubic centimeters of 2.5 per cent sterile sodium citrate is then drawn into a syringe and instilled into the container, being allowed to run through the tubing (Fig 2B) through which the blood is to flow into the container. A tourniquet is then applied to the donor's arm and the needle at the end of the collecting tubing inserted into the vein (Fig 2). The container is held a few inches below the level of the donor's arm to facilitate the flow of blood. It is gently agitated to allow for mixing with the citrate. The container is filled to the top with



blood (Fig 1B) If two containers are to be filled the tubing leading from the donor's arm is pinched off, the needle withdrawn from the vaccine cap, and inserted through the cap of the second container which may be filled in the same manner The needle and air vent are then withdrawn from the vaccine cap of the container and a rubber cap drawn over the vaccine cap and neck of the container after it has been cleansed with iodine and alcohol (Fig 3A)

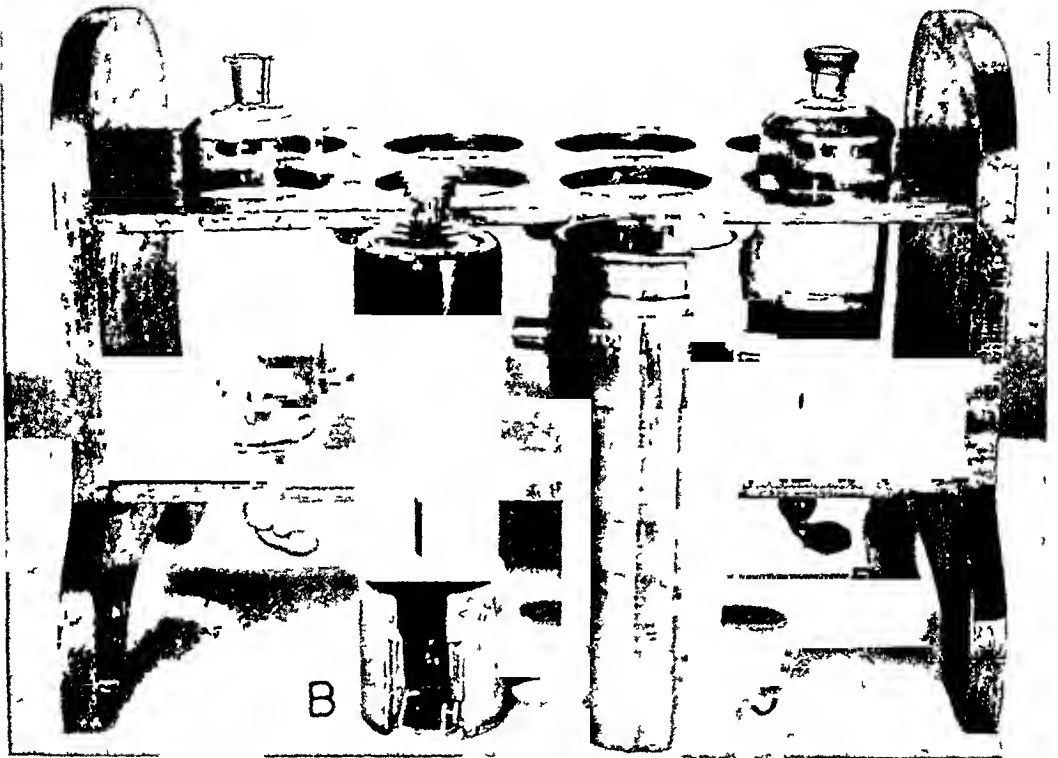


FIG 1—A Empty container showing needle hole in lower bulb for drawing off the cells  
B Container assembled and filled with blood ready to be placed in trunion cup  
C Special trunion cup made to receive the container  
D Container after first centrifugation Cells separated from plasma C clamp removed from lower bulb

The filled containers are now ready for centrifuging They are placed in especially designed trunion cups (Fig 1C and 4A) and rotated at 1200 revolutions for 20 minutes The container is supported by a block of hard wood which is shaped to fit its curved under surface, and prevents the bulbs from touching the bottom of the trunion cup (Fig 1B) To prevent the force of centrifuging from forcing any blood out around the rubber tubing over the needle hole in the smaller bulb at the bottom of the container, a C clamp (Fig 1B) is placed over the small bulb and tubing and is tightened against this opening to seal it firmly (Figs 3A and B) The C clamp is removed after centrifuging is completed To draw off the packed cells the container is placed in a ring stand (Fig 4B) The rubber tubing over the smaller bulb is cleansed with iodine and alcohol, and a sterile needle introduced into this bulb through the rubber tubing and needle hole An air filter is placed through the vaccine cap at the top to allow for fall in

## PREPARATION OF BLOOD PLASMA

fluid level within the container. The cells may be drawn into physiologic sodium chloride solution and used for transfusing anemia patients.

After the packed cells are all withdrawn, some will be found to adhere to the side of the container. Therefore, the needle is withdrawn, and the container removed from the ring stand. The one-inch (2.5 cm) piece of



FIG 2—Blood from donor being collected into assembled container. A Air vent. B Collecting tubing.

tubing over the lower bulb is slightly rotated to bring a new surface of rubber over the hole in the bulb where the needle was inserted for drawing off the cells. The C clamp is again put in place as before, and the container agitated to free the cells adhering to its walls and resuspend them in the plasma. It is again placed in the centrifuge and rotated for ten minutes at 1200 revolutions per minute. This will force the remaining cells into the two lower bulbs. After this second centrifugation the container is turned end for end, so the bulb portion is uppermost, and supported in the ring stand (Fig 5). The packed cells in the bulbs will not run down through the narrowly constricted portion, but will remain trapped within the two bulbs. The plasma is withdrawn by a needle and air vent being inserted through the vaccine cap, after the cap has been cleansed with iodine and alcohol. The air vent is held above the plasma level as shown (Fig 5).

When the plasma of six to eight donors is pooled it is placed in the ice box for 12 hours or more. It is finally racked off into sterile physiologic

sodium chloride plus dextrose solution (Fig 6) During this process it is passed through a 200-mesh filter (Fig 6A) to remove fibrin clots A Kaufman syringe serves as a very satisfactory valve for shutting off the flow of plasma when receptacles are to be changed during the procedure

DISCUSSION —Many methods have been devised for the separation and pooling of human plasma for therapeutic use Most previously described methods depend upon siphoning the plasma from a container with a large

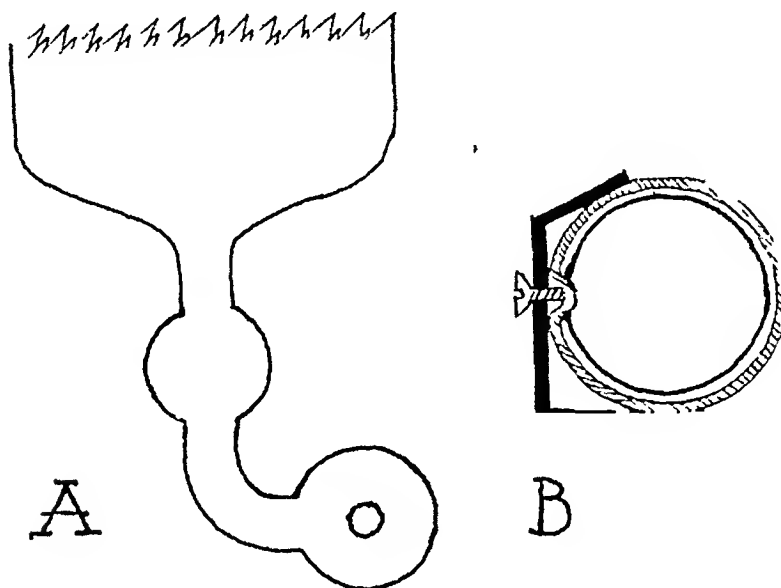


FIG 3 —A Diagram of the lower portion of container showing needle hole in lower bulb  
B Cross section diagram of lower bulb to show how screw of C clamp forces rubber tubing into needle hole to seal it firmly

plasma-cell interface Scudder was the first to improve the yield by designing a container with a relatively small area at the junction of the plasma and the cells Crowley, in 1940, described a container with an even greater reduction in plasma-cell interface However, this method necessitates the determination of cell volumes on each donor to give a good plasma yield Furthermore, it presents the difficulty of adequate citration of the blood, and is expensive because each ampoule can be used only once The separation container which we have designed has been based upon the principle of small plasma-cell interface, but obviates the objections described above

Some investigators with whom I have discussed this type of container believe that forcing the cells through a narrow constriction by means of centrifugation would tend to rupture many of the cells, and allow their content to flow into the plasma Experience with this, and similar types of containers, have proven this false We believe that a clearer plasma is obtained by centrifuging and pooling the plasma the same day than by the commonly employed method of placing the citrated whole blood in the ice box for a period of time and allowing the cells to settle from the plasma by gravity

## PREPARATION OF BLOOD PLASMA

### SUMMARY

An improved method for collecting, centrifuging and pooling human blood plasma has been described. The yield by this method has been consistently 10 to 15 per cent greater than by any method with which we are familiar. No difficulties are encountered in obtaining satisfactory mixing of the citrate with the blood, cell volumes of donors need not be determined,

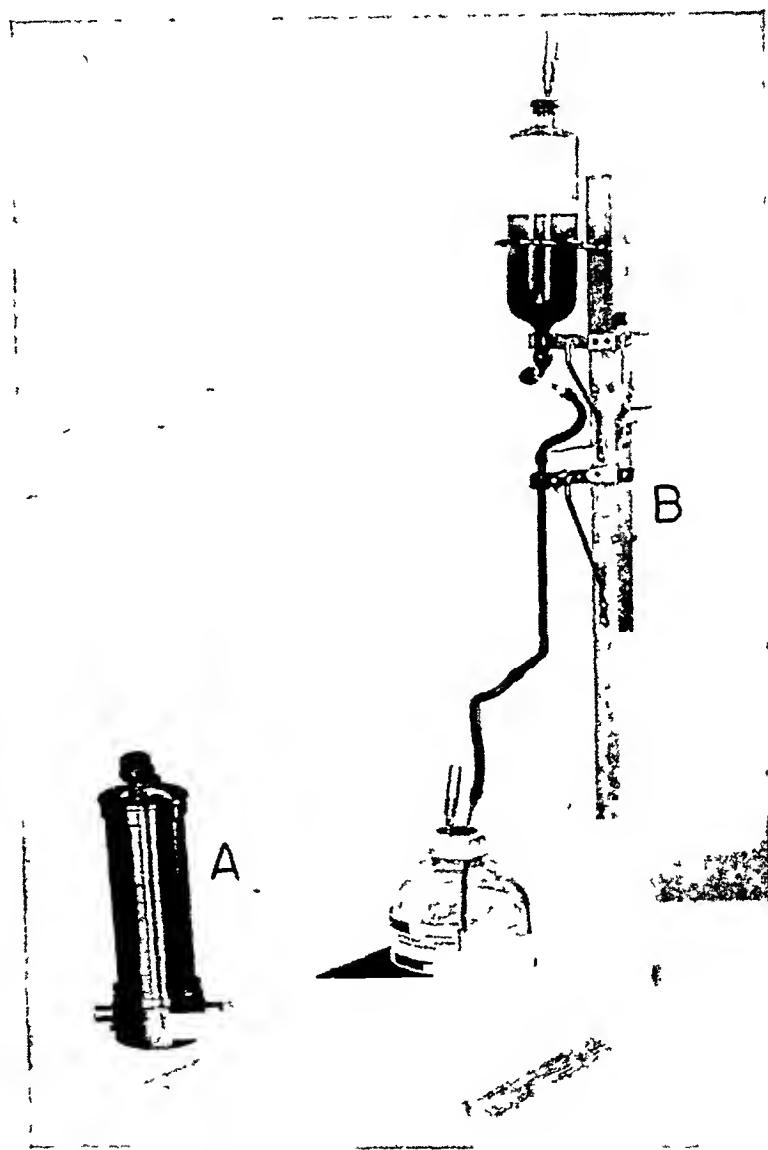


FIG 4—A Trunion cup with container after removal from centrifuge

B Container held in ring stand. Needle inserted through rubber tubing over lower bulb for drawing off packed cells. Air vents in place. Plasma is not clear above cell layer because some of cells adhere to sides of container.

and the same container can be used repeatedly. This method requires no containers with a vacuum, as is frequently advocated by other investigators. The method is a completely closed one, and the plasma can be separated and pooled on the same day the blood is collected, with minimal disintegration of red blood cells during the procedure. The blood cells can easily be preserved for transfusing anemia patients. The same principle could be used in designing containers to hold a larger volume of blood.

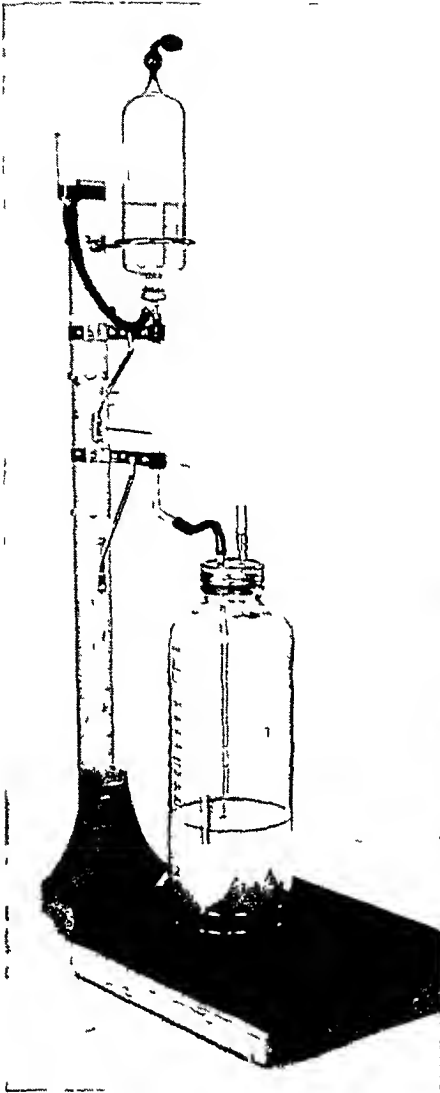


FIG 5

FIG 5—Plasma being drawn off into pooling bottle. Air vents in place. Blood cells trapped in bulbs at upper end of container.

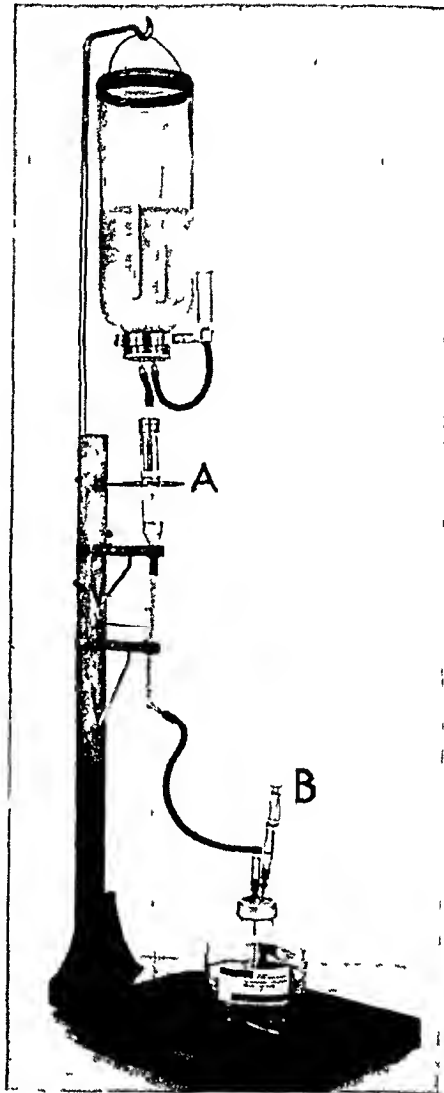


FIG 6

FIG 6—Plasma being drawn from pooling bottle into smaller flasks. A Filter. B Kaufman syringe.

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# THE PERIPHERAL CIRCULATION DURING THE TOURNIQUET SHOCK SYNDROME IN THE RAT\*

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AMONG RECENT INVESTIGATIONS on circulatory failure in tourniquet shock, at least two have dealt with microscopic observations of the mesenteric blood vessels remote from the site of the damage inflicted<sup>1, 2</sup> These observations were confined to changes in caliber of the vessels and rate of the blood flow The capillaries were referred to, but in neither paper was consideration taken of the possibility that the capillary bed possesses several vascular components, each playing a specific rôle in the functional activity of the capillary bed as a whole

This aspect of the capillary bed and the significance of its specific reactions have been recently worked out in detail for the normal mesenteric circulation of the dog and rat<sup>3</sup> Moreover, the observed reactions have proven to be sufficiently critical for use in following the progressive changes caused by hemorrhage and in enabling one to distinguish the effects of acute<sup>4</sup> from those of graded hemorrhage<sup>5</sup>

The application of a tourniquet to an extremity and its subsequent release is a method of inducing, with a minimum of direct trauma, a considerable reduction in blood volume through the loss of fluid into the damaged limb (Wilson and Roome<sup>6</sup>) Some investigators have attributed the resulting shock syndrome and eventual death of the animal mainly to the fluid loss<sup>7, 9</sup> Others have indicated that the syndrome includes either the presence of a toxic factor<sup>10, 11, 12</sup> or the absence of some ingredient of the blood lost to the damaged tissue<sup>13</sup>

The sensitive responses of the capillary bed offer a method of distinguishing between the mechanical effects of fluid loss and the toxic effects of abnormal conditions in the blood stream<sup>16</sup> Furthermore, the responses of the peripheral circulation, since they deal with the components of the vascular system with

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\* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York University It was also supported in part by the Lilly Research Laboratories, Woods Hole, Massachusetts It constitutes the sixth of a series of studies on experimentally induced shock The first study is listed as No 3, the third as No 14, the fourth as No 4 and the fifth as No 5 in the bibliography of the present paper The second study, on the Noble-Collip rotating drum trauma, appeared in *Am J Physiol*, 139, 123, 1943

which the circulatory failure is primarily concerned, make it possible to determine the relative importance of these two factors in the syndrome

This paper deals with a microscopic study of the circulatory changes in the meso-appendix of the rat under nembutal anesthesia, after the release of a tight tourniquet placed around the thigh for a protracted period of time

### METHOD

The rats varied in weight from about 150 to 200 Gm. In most of the experiments the tourniquet was applied to one hind limb only, a rubber band being wrapped as high as possible around the thigh to occlude all flow without thrombosing the blood vessels. This was done on the unanesthetized rat held in a specially constructed cage, for which we are indebted to Dr. F. M. Allen. About half an hour before release of the tourniquet, the rats were given an intramuscular injection of sodium pentobarbital (2-3 mg./100 Gm. body-weight), known commercially as nembutal. The meso-appendix was then exposed for microscopic observation. The peculiar advantage of the meso-appendix for a study of the capillary bed has been presented in our recent paper,<sup>3</sup> together with means for minimizing the effects of the operation involved in the exposure. The essential precautions are minimum handling of the intestine and constant irrigation of the exposed tissue with warm gelatin-Ringer's solution\*. When properly prepared the tissue is serviceable for continuous observation over a period of several hours.

Simultaneously with the observations on the meso-appendix, blood pressure determinations were periodically made by using a pneumatic rubber cuff around the thigh of the limb not subjected to the tourniquet.<sup>14</sup> Hematocrit readings by the Van Allen method were also taken.

Prior to release of the tourniquet, the meso-appendix was always examined to establish the normality of its circulation. The chief criteria of normality were (a) a relatively sporadic flow in the capillaries and a restriction of most of the blood to the central channels leading from the arterioles to the venules, and (b) a general, nondilated state of the muscular vessels of the bed. A good test for the normal state was the application of a few drops of histamine in gelatin-Ringer's solution (1:10,000 to 1:100,000) to the surface of the meso-appendix. This should produce a temporary dilatation of the vessels and an appreciable increase in the extent of the capillary flow. If the trauma incidental to handling the intestine has been excessive, the vessels already will have been dilated to the extent that the effect of the histamine at this concentration will be negligible.

The criteria<sup>5</sup> for noting the progressive changes in the circulation following release of the tourniquet were (a) changes in the distribution and rate of flow in the capillary bed, (b) changes in caliber of selected arterioles (15-20 micra in diameter), (c) augmentation or diminution of the vasomotion

\* This had the following constitution in grams-per cent in water: Granular ash-free gelatin, 1, NaCl, 0.8, KCl, 0.02, CaCl<sub>2</sub>, 0.02 and NaHCO<sub>3</sub> sufficient to bring the solution to pH 7.2-7.4.

of the metarterioles,\* and (d) change in the reactivity of the metarterioles to the local application of epinephrine. This last criterion was tested by determining the minimal concentration of epinephrine required to produce a partial narrowing of the muscular components of the capillary bed. In normal rats, anesthetized with a minimum effective dose of sodium pentobarbital, this was 1 part epinephrine in 1 million or in 2 million parts gelatin-Ringer's solution.

#### EXPERIMENTAL RESULTS

The tourniquet was applied to one hind limb for periods of 3, 5, 7 or 8 hours. In two cases the tourniquet was applied to two hind limbs for 5 hours. Only those rats were considered in which release of the tourniquet was followed by a return of the circulation in the occluded limb. The accompanying table gives the number of rats studied, the survival time and the percentage of fatalities in each group of the several periods with one-limb tourniquet (Table I).

TABLE I

No. of Rats	Time in Hours of Tourniquet Application	Survival Time in Hours of Fatal Cases after Tourniquet Release	No. of Fatal Cases
9	3-4	4-5	3
38	5-6	3 5-4	29
6	7	2 5-3	5
3	8	2-2 5	3

After removal of the tourniquet, changes appeared in the circulation of the meso-appendix, which could be classified into three successive, well-defined stages. An initial hyperemic, an hyperreactive, and an hyporeactive stage. The duration and intensity of the changes and the relative lengths of the stages were found to vary with the duration of the period of tourniquet application. The following is a summarized description of the effects observed.

#### *Tourniquet Applied for Three to Four Hours*

(9 rats, of which 3 succumbed)

1 *Initial Hyperemic Stage* (duration, 20-30 minutes after tourniquet release) —Within a few minutes after release of the tourniquet, the blood pressure fell precipitously from 120 Mm to about 80 Mm Hgs and then slowly rose after 4 to 5 minutes until, within 30 minutes, it had reached about 100 Mm. During the abrupt fall, the heart rate was considerably slowed.

In the meso-appendix the release was followed within one to two minutes by a marked dilatation of all the muscular vessels, especially noticeable in the larger arteries and veins (100-150 micra), which dilated to about one-

\* The metarterioles are the terminal, discontinuously muscular vessels leading from the arterioles and constitute the proximal segment of the central channels in the capillary bed. The metarterioles and their precapillary offshoots normally exhibit a vasomotion consisting of alternating constrictor and dilator phases at irregular intervals of 30 seconds to 3 minutes. (Refer for further details to reference 3)



half more than their original diameters. The vasodilatation was accompanied by a change of the normally restricted capillary circulation to an over-all hyperemic state, with a significant slowing of the flow, especially on the venous side of the capillary bed.

This stage lasted about 20 to 30 minutes, and the hyperemia passed off as the blood pressure began to rise with appreciable acceleration of the blood flow in the capillary bed.

Leukocytes were seen sticking in increasing numbers to the inner walls of the capillaries and venules. Further evidence that the endothelial walls were being affected at this stage was the formation of minute petechiae with extravasation of red cells in some areas of the capillary bed.

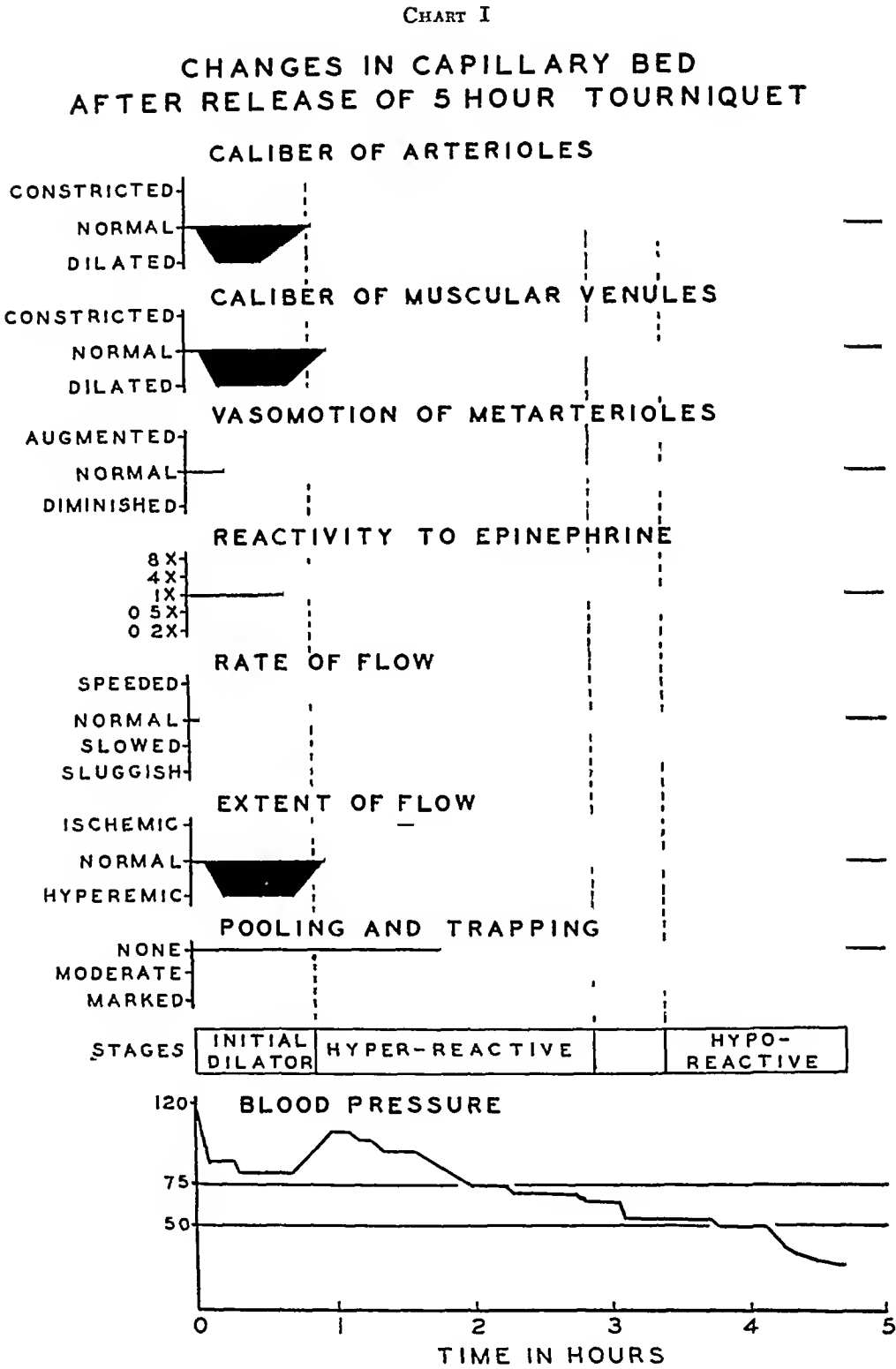
2 *Hyperreactive Stage*—About 30 minutes after release of the tourniquet the blood pressure again began to fall, but this time gradually and to a level as low as 60 Mm Hg. This was accompanied by a progressive swelling of the damaged limb over a period of about two hours.

The arteries and veins underwent a continually increasing constriction until, at the time of the maximal swelling of the damaged limb, they had been reduced to about one-third their original diameters. The two outstanding reactions in the capillary bed were an augmentation of the vasomotion and an hyperactivity of the vessels to the topical application of epinephrine. The vasomotion of the metarterioles and precapillaries became increasingly frequent and pronounced. This restricted the flow to the central channels so that the true capillaries became relatively anemic. The hyperreactive condition was indicated by the fact that epinephrine in concentrations as low as 1:10 million to 1:20 million caused an immediate constriction of the metarterioles, whereas, a similar reaction prior to removal of the tourniquet could be obtained only with a concentration of 1:2 million. This hyperreactivity persisted for almost three hours. The blood pressure had now fallen to 60–65 Mm Hg and the flow through the capillary bed was considerably slowed, especially on the venous side of the bed. Hematocrit values of blood samples obtained from the jugular vein of the fatal cases reached 55 to 60 per cent.

Except for the hemoconcentration, the reactions of the capillary bed throughout this period, *viz.*, constriction of the larger vessels, augmented vasomotion of the metarterioles and hyperactivity to epinephrine, were similar to those occurring in acute hemorrhage.<sup>4</sup>

In the six rats which eventually recovered, the normal unidirectional flow through the bed, although considerably slowed, was never lost. The circulation through the bed began to improve and the blood pressure returned to normal within four to five hours after release of the tourniquet.

In the three rats which did not recover, the flow in the capillary bed became increasingly sluggish while much of the blood by-passed the bed through arteriovenous anastomoses. The blood pressure continued to fall and at about 50–60 Mm Hg, there developed an increasingly persistent backflow from the venules into the capillary bed. The consequent pooling and stagnation of blood in the capillaries resulted in an abrupt collapse of the peripheral circulation and, within five to ten minutes, was followed by



death of the animal During this entire period the epinephrine reactivity remained hypernormal, both in the rats which eventually recovered and in those which succumbed, the reactivity in the latter persisting until a few minutes before death

No definite hyporeactive stage appeared in this group

*Tourniquet Applied for Five to Six Hours*

(38 rats, of which 29 succumbed)

A tabulation of the reactions taken from the protocol of a rat typifying the effect of a five-hour tourniquet is given in Chart 1 The following is a general summary of the reactions of the rats of this group

1 *Initial Hyperemic Stage* (duration 30-40 minutes after tourniquet release) —This period of hyperemia and vascular dilatation was similar to that described in the preceding experiment except that it was more intense and of longer duration Pronounced leukocytic sticking lasted for 20 to 30 minutes and was accompanied by the appearance in the circulation of small clumps of red and white cells These emboli frequently plugged vessels in the capillary bed but soon were dislodged as the general hyperemia persisted The swelling of the damaged limb began before the initial hyperemic stage had disappeared

2 *Hyperreactive Stage* —The development of an hyperreactivity occurred before the initial hyperemic stage had passed off This could be detected by the augmentation of the metarteriolar vasomotion and the appearance of an increased reactivity to epinephrine, while the larger vessels were still dilated and the capillary flow was hyperemic

A well-defined hyperreactive stage, with a generalized ischemia and a slowed capillary flow, became evident within an hour and a half after release of the tourniquet and lasted for about 45 to 60 minutes The flow in the capillary bed became considerably slowed before the blood pressure had fallen to 55 to 60 Mm Hg Hematocrit values attained 60 per cent

3 *Hyporeactive Stage* —A change to the hyporeactive condition began to develop while the capillary flow was still unidirectional, although becoming increasingly sluggish The epinephrine reactivity fell below normal and vasomotion of the metarterioles disappeared while the arterioles were still partially constricted The capillaries, which prior to this were anemic, now began to contain blood throughout the bed

In the 29 rats which eventually died this was followed several minutes later by a dilatation of the muscular metarterioles and precapillaries of the bed A backflow from the venules developed, still further filling the capillaries with static blood By this time the blood pressure had fallen below 40 Mm and death generally occurred about 4 5 to 5 hours after release of the tourniquet

Throughout the hyporeactive period, the larger arteries and veins remained constricted as in the hyperreactive stage Dilatation of these larger vessels was a terminal phenomenon and occurred only 15 to 20 minutes before death

Of the nine rats which survived, the circulation never went beyond the initial phase of the hyporeactive stage. The critical features for survival appeared to be the persistence of a unidirectional flow and the resumption of vasomotion after a transient cessation of not more than 20 to 40 minutes.

*Tourniquet Applied for Seven to Eight Hours*

(9 rats, all of which succumbed)

The initial hyperemic dilator stage appeared immediately after release of the tourniquet and was followed within a few minutes by a slowing of the blood flow. The swelling of the damaged limb appeared early and was accompanied by a partial constriction of the larger arteries. Hemoconstriction was moderate, the hematocrit values not exceeding 50 per cent. The initial dilator stage, with normal reactivity to epinephrine, lasted at least 45 to 50 minutes and in the eight-hour tourniquet experiments approached two hours. The hyperreactive period was not prominent, and, especially in the eight-hour experiments, the initial dilator stage passed directly into the hyporeactive stage, the reactions of which were more profound than those in the five- to six-hour experiments. The capillaries became markedly congested with widespread vasodilatation, and death occurred within two to three hours after release of the tourniquet.

The failure of the circulation to return to the damaged limb after release of the tourniquet occurred more frequently when the tourniquet was applied for more than six hours. Rats in which this occurred showed none of the circulatory changes described above.

*Tourniquet Applied for Five Hours to Two Hind Legs*

Only two rats were treated in this manner. The initial hyperemic dilator stage developed within one minute after release of the tourniquets and disappeared 10 to 15 minutes later. Swelling of both legs became appreciable before the hyperemic stage had disappeared. During this period there was a marked vasoconstriction of the arteries and arterioles and a pronounced vasomotion of the metarterioles. The epinephrine reactivity rose from 1:2 million to 1:10 to 15 million and persisted until a few minutes before death, 2.5 to 3 hours after release of the tourniquet. Except for the initial dilator stage and the subsequent hemoconcentration, the reactions of the capillary bed closely resembled those of severe acute hemorrhage.

DISCUSSION—The two factors to which the changes in the tourniquet shock syndrome have generally been ascribed are fluid loss and the elaboration of so-called toxic substances. Our experiments have shown that the peripheral circulatory collapse can occur either with both factors contributing significantly or with one or the other predominating, the relative effectiveness of the two factors varying with differences in the duration of the application of the tourniquet. The shorter the duration, the more predominant were the mechanical effects of fluid loss and the less were the indications of a toxic factor. On the other hand, the longer the duration of the tourniquet, within limits, the more predominant were the toxic manifestations.

The five- to six-hour period of applying the tourniquet to one hind limb

produced changes in the visceral vascular bed which most nearly approached those observed in irreversible hemorrhagic shock.<sup>5</sup> These were an hyperreactivity followed by an hyporeactivity of the capillary bed. The initial hyperemic stage appears to be peculiar to the tourniquet type of shock.

Of special interest in tourniquet shock is the difference between the circulatory reactions immediately following release of the tourniquet and those appearing in the later stages of the shock syndrome. Both are dilator responses of the muscular vessels of the capillary bed but, whereas, the first is accompanied by a developing hyperreactivity, the latter is associated with a definite hyporeactivity of the vessels. Both reactions are undoubtedly related to changes which occur in the damaged limb. The first appears after a period of tissue anoxia and some muscle damage caused by the pressure of the tourniquet cord, the second, after the fluid loss into the limb.

The initial dilator stage occurred in all the rats, irrespective of whether they died or survived, while the latter typically appeared only in rats which eventually succumbed.

*Initial Hyperemic Stage and Hemoconcentration*—Immediately following removal of the tourniquet, the reactions of the vessels in the meso-appendix suggest the release of dilator substances into the blood from the damaged limb. These, although temporary in their effect, may predispose the blood vessels to the development of the hyporeactivity which appears later. The effect of the initial dilator phase and the hemoconcentration, with the resulting increased viscosity of the blood, in tourniquet shock, may explain the reduction in flow through the capillary bed at an earlier stage of hypotension than that which obtains after hemorrhage.<sup>5</sup> Thus, an animal in hemorrhagic hypotension with a blood pressure of 60 Mm. still has an adequate though markedly slowed peripheral circulation. On the other hand, at a similar blood pressure level in tourniquet shock the capillary circulation is usually on the verge of becoming disrupted.

*Hyperactive Stage*—This stage in the tourniquet experiments, except for possible subsidiary effects of hemoconcentration and the initial and transitory dilator reaction, resembled that found early in rats subjected to hemorrhage.<sup>4, 5</sup> In the three- to four-hour tourniquet experiments this type of hyperreactivity predominates throughout. Fatality is low and, in the rats which succumb, the collapse of the circulation can be ascribed primarily to the mechanical effect of the fluid loss.

The mechanical effect was found to be still more predominant when two limbs were ligated. Considered superficially, it would seem that damage to a larger mass of muscle should predispose the animal to a more toxic type of shock. However, two limbs also offer a larger site for fluid loss. The fluid lost is excessive and the consequent hyperreactivity continues until the rats die from the mechanical effects of circulatory collapse before the development of hyporeactivity.

*Hyporeactive Stage*—Our observations on complete tourniquets and those of Page and Abell<sup>2</sup> on venous tourniquets agree regarding the development and persistence of vasoconstriction of the larger blood vessels throughout

most of the syndrome. However, our observations lead us to infer that, accompanying the widespread peripheral ischemia, the capillary circulation develops an autonomy and reacts differently from the remainder of the circulatory system. This is indicated by the fact that the muscular vessels of the capillary bed, as seen in the meso-appendix, relax while the larger vessels do not.

The independence of action of the capillary bed seems to be related to conditions developed in the ischemic tissues. These conditions would appear to serve as a local mechanism for increasing blood flow to the tissues. However, at this stage of the shock syndrome the circumstances of diminished blood volume and low blood pressure are such as to allow of no significant increase in flow. As a result, therefore, the hyporeactive state of the capillary bed eliminates its compensatory action against fluid loss and thus negates the compensatory effect of the widespread vasoconstriction elsewhere. The actual amount of blood which is present in the peripheral vessels may be less than in normal animals, as Fine and Seligman<sup>15</sup> have shown, but the blood which reaches the bed becomes pooled there. This aggravates the general anoxemia and contributes to the circulatory collapse. The late dilatation of the arteries in the cat's mesentery described by Page and Abell<sup>2</sup> occurs only in the terminal stages of the collapse and is not to be confused with the hyporeactivity in the capillary bed which appears earlier.

One of the chief features in the development of the hyporeactive stage is a long-continued maintenance of a much slowed peripheral circulation. This stage tends not to occur after a relatively short tourniquet application to one hind limb or after a longer application to two hind limbs. The slowing of the peripheral flow resulting from application of the tourniquet to one hind limb for a relatively short period of time (three to four hours) usually is insufficient to cause circulatory collapse. The condition resembles that of moderate acute hemorrhage. The few rats which succumbed were probably highly susceptible to fluid loss. Susceptibility of this sort is discussed in a previous paper.<sup>5</sup> When two hind limbs were occluded, even for relatively long periods, the condition resembles that of severe acute hemorrhage. The fluid loss is so great as to induce circulatory collapse while the capillary bed is still in the hyperreactive state. A tourniquet application of five to seven hours to one hind limb is the optimum treatment for inducing a well-defined hyporeactive stage following the hyperreactive stage.

Since the reactions were observed in the meso-appendix remote from the site of the inflicted injury and since they occurred only if the circulation was reestablished and was maintained for a protracted period of time, it is logical to infer that, at least one of the factors responsible for the observed effects is the transmission of a substance or of substances from the damaged limb. Objective evidence for the presence of such substances in the blood of shocked animals has been presented in a preliminary paper.<sup>16</sup> The relation of these substances to those producing the toxic effects obtained in dogs by Blalock,<sup>12</sup> and Katzenstein, Mylon and Winternitz,<sup>10</sup> is not clear. Both of these investigations were conducted by noting the effect of the intravenous injection

into normal dogs of thoracic lymph obtained from injured dogs Blalock performed crush injuries on one hind limb of dogs under either morphine or nembutal and collected the lymph for hours before and after the injury Some of the recipient dogs died, a few with a significant fall in blood pressure and a few with casts in the urine Katzenstein, Mylon and Winternitz used complete tourniquets on two hind limbs of dogs anesthetized with nembutal The injection of lymph from these dogs (time of obtaining not recorded) produced a blood pressure fall in nine out of 18 recipient dogs In our experiments a prime feature for ascertaining the existence of a so-called toxic factor was the change in reactivity of the capillary bed in which the vascular components become functionally depressed

Allen<sup>11</sup> observed that, the longer the period of tourniquet application, the more difficult it was to save the animal by fluid therapy He intimated that the development of a toxic factor would help to explain the fatal results of prolonged tourniquet application However, he stressed the fluid loss factor because the fatal results obtained by ligating a larger muscle mass (*e g*, two hind limbs) frequently could be avoided, by fluid therapy alone Actually, the animals subjected to a one hind limb tourniquet should not necessarily be compared with those subjected to tourniquets on two or more hind limbs The fact that Allen found the latter to be amenable to fluid therapy supports the view that their death is due chiefly if not entirely to excessive fluid loss

An alternative to the presence of a toxic factor has been presented by Selye and Dosne<sup>13</sup> from their experiments on tourniquet shock in monkeys and cats They found that damaged tissues utilize certain substances (*e g*, sugar) more actively than the corresponding normal tissues They suggested that the symptoms following release of the tourniquet are "not because substances coming from the limb poison the rest of the body but because active metabolic processes drain the body of certain essential compounds, the lack of which causes shock"

Selye and Dosne also tested for the presence of toxic substances in the blood from the damaged extremity by injecting the blood into adrenalectomized rats By using death-rate as a criterion they found no difference between this and the blood of normal animals From this they concluded that no special toxicity could be demonstrated in the blood derived directly from a leg so severely damaged by anoxia that, had its circulation been reunited with the rest of the body, severe shock would have developed

Adrenalectomized rats are known to be highly sensitive to a variety of toxins We have found (unpublished observations) that such rats are not suitable for testing substances which depress the peripheral circulation since the operation alone causes the capillary bed to become hyporeactive to epinephrine and to exhibit no vasomotion This would render such rats inadequate as tests for substances which induce hyporeactivity of the capillary bed, since the response to be looked for is already present in the test animal

Evidence for a toxic factor in traumatic shock has generally been obtained from animals anesthetized during the procedure of inducing the shock Katzenstein, Mylon and Winternitz<sup>10</sup> have indicated that the dosage of

nembutal must be carefully controlled to minimize the vasodepressor effect of the drug. In the experiments described in this paper the rats were not anesthetized for the tourniquet application but only for the exposure of the meso-appendix, a single minimal effective dose of nembutal being administered shortly before exposing the meso-appendix. The subsequent comatose state of the animals during the shock syndrome obviated further medication. Even with such precautions it is to be expected that the anesthetic will exert some effect. Fine and Seligman<sup>15</sup> stress this feature and claim that morphine (3 mg/Kg) does not have the deleterious effects of typical anesthetics. In defense of our use of sodium pentobarbital it may be stated that in our experiments on graded hemorrhage in dogs<sup>5</sup> the capillary circulation of the omentum exhibited the same succession of events (hyperreactivity followed by hyporeactivity) irrespective of whether the dogs had been immobilized with morphine or with the barbiturate. In a recent paper<sup>17</sup> we have presented the effects of different anesthetics on the capillary circulation in the omentum of hemorrhaged dogs. With sodium pentobarbital the effects were more marked and appeared earlier in the hemorrhagic syndrome than when morphine was used. However, the succession of events was identical and the hyporeactive stage of the capillary bed developed under both types of treatment.

#### SUMMARY

During the shock syndrome after release of a tourniquet applied to one hind limb for five to six hours, the peripheral circulation in the rat's meso-appendix undergoes the following changes, provided circulation returns to the limb. These changes are classified into three successive stages.

I *Initial Dilator* —The initial dilator stage appears within a few minutes after release of the tourniquet and is more prominent the longer the tourniquet has been applied. It is characterized by (1) abrupt fall of blood pressure followed by a rise which does not reach normal levels, (2) widespread vasodilatation and hyperemia with slowed capillary flow, (3) leukocytic sticking and development of minute extravasations observed in the capillary bed, (4) normal reactivity of the capillary bed to the topical applications of epinephrine, and (5) in most cases, persistence of the vasomotion of the metarterioles.

II *Hyperreactive* —The hyperreactive stage appears when the damaged limb begins to swell. The following changes are commensurate with the extent of swelling: (1) Continued fall in blood pressure, (2) increased hemoconcentration and further slowing of the capillary flow, (3) hyperreactivity to epinephrine, and (4) widespread vasoconstriction of the larger vessels and augmented vasomotion with restriction of the capillary flow to the central channels of the capillary bed.

III *Hyporeactive* —The hyporeactive stage appears proportionately earlier the longer the tourniquet has been in place. It is characterized by (1) fall in blood pressure to below 60 mm Hg, (2) hyporeactivity of the capillary bed to epinephrine, (3) complete loss of vasomotion, and (4) over-all sluggish capillary flow followed by stagnation, venular backflow and finally a collapse of the circulation.



When the tourniquet has been applied for three to four hours the capillary bed maintains its hyperreactive state throughout. The rate of capillary flow becomes greatly reduced but in the majority of cases, the normal directional flow is maintained and the circulation progressively improves. In the few cases which succumb, the hyperreactivity persists to within a few minutes before death.

When the tourniquet has been in place for six hours, or longer, there is a tendency for the hyperreactive stage to be shorter, the longer the duration of the tourniquet application. In some cases, the initially hyperemic capillary bed with its dilated vessels may pass directly into the hyporeactive phase.

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# PROPOSED ALTERATION IN THE KNEE JOINT OF PROSTHESIS FOR BELOW-KNEE AMPUTATION

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THE PURPOSE of this paper is to point out certain facts that were observed while treating a patient with an infection of a below-knee stump. The patient, an officer in the Air Corps, received a G S W of the right leg in August, 1942, which necessitated a below-knee amputation, leaving a four-inch tibial stump. He was fitted with a prosthesis and was able to walk without any appreciable limp. He stated, however, that while flying a plane or driving a car there was an excessive amount of pressure and irritation to the anterior tip of the stump. This resulted in so much pain at times that he would have to turn over the controls to his copilot or suffer considerable pain for the following 24 to 48 hours. Several attempts at readjustment of the leg by the manufacturers did not alter the situation.

In order to visualize the true nature of the patient's complaint roentgenograms were taken with the prosthesis in place (1) with weight-bearing, (2) nonweight-bearing, knee extended, and (3) nonweight-bearing and knee flexed. Figure 1 is a tracing of the roentgenogram taken in position 3, *c g*, nonweight-bearing and knee flexed.

It is at once obvious that any attempt to extend the prosthetic leg would cause practically all of the pressure to be exerted at point E (Fig 1). The reason for this is likewise obvious when lines A-B and C-D are superimposed on the drawing. These lines represent the long axes of the prosthetic leg and the stump, respectively. The prosthetic leg is flexed  $90^\circ$ , whereas the tibial stump is only flexed  $60^\circ$ - $70^\circ$ . This, in turn, is caused by the fact that the axis of the prosthetic joint is distal to the axis of the knee joint. Consequently, during the process of flexion the prosthetic joint swings through an arc of  $90^\circ$ , while the stump is only allowed to swing through an arc of  $60^\circ$ - $70^\circ$ . Thus, instead of the long axes of the stump and prosthesis remaining parallel they become angulated and an excessive pressure is brought to bear at point E where the front end of the stump contacts the anterior surface of the prosthesis.

Having analyzed the cause of the unequal distribution of pressure on the end of the stump, it would seem a very easy matter to correct the fault by merely changing the position of the axis of the prosthetic joint to coincide with that of the knee joint proper. That the solution to this problem is not quite so easy will be illustrated by studying Figures 2 and 3. Figure 2 is a tracing of a roentgenogram with the knee extended and the patient bearing weight on the leg. Figure 3 is a similar tracing without weight-bearing. Note that in Figure 2 the axes of the prosthetic knee joint and that of the



knee joint proper are approximately superimposed. When weight is removed from the prosthesis the prosthetic joint (along with the entire prosthesis) slides distally 1.5 inches (see Fig. 3), throwing the two joint axes out of alignment. It is in this latter position of malalignment that one finds the prosthesis when flexion is required. Compare the relative positions of the prosthetic joints in Figures 1 and 3.

The fact that the prosthesis slides distally when there is no weight-bearing is not due in any way to an improper fit. It must be remembered that weight-bearing with this type of prosthesis is transmitted to the upper thigh and tuberosity of the ischium. When the weight is borne on the prosthesis

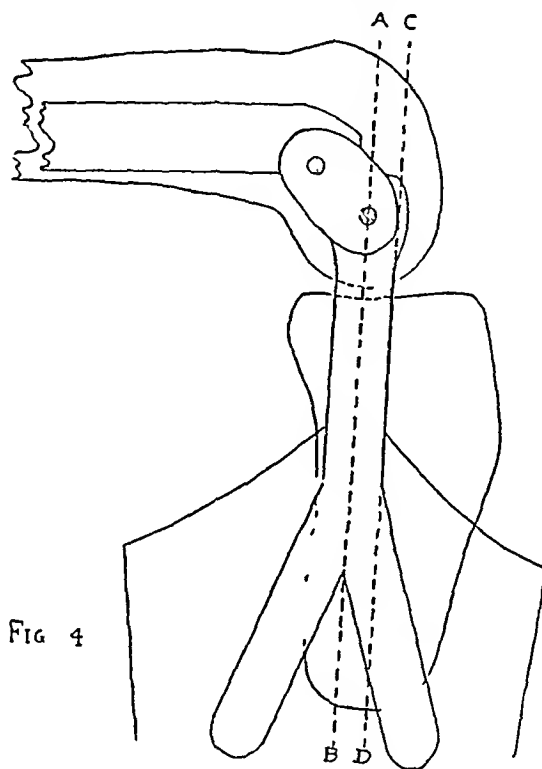


FIG. 4

there is considerable give and compression of the soft tissue in the region of the weight-bearing surfaces. The soft tissue compression in this patient amounted to 1.5 inches. Consequently, when weight is removed from the prosthesis, no matter how perfect the fit, it slides off the thigh distally.

One solution to the problem would be to alter the position of the prosthetic joint to a higher level by shortening the upper brace 1.5 inches and lengthening the lower brace a similar amount. Thus, during weight-bearing the axis of the prosthetic joint would lie 1.5 inches proximal to that of the knee joint proper, but when weight was removed the prosthesis would slide distal, and the two joints' axes would for all practical purposes coincide.

Figure 4 is a tracing of a model so designed. It will be noted that the long axes of both stump (C-D) and prosthesis (A-B) are parallel. The tibial crest is parallel to the front of the prosthesis, thus, giving a broad pressure-bearing surface instead of a pressure point, as in E (Fig. 1). This is not a satisfactory solution, however, because the lower brace is so long the stump and prosthetic socket nearly disengage during flexion.

We now have the two factors of the problem which must be dealt with (1) Under conditions of nonweight-bearing the joint axes of the artificial leg and the knee joint proper must approximate a common plane, this plane must be at right-angles to the long axis of the femur (2) The leg portion of the prosthesis must not be allowed to slide off the stump during flexion

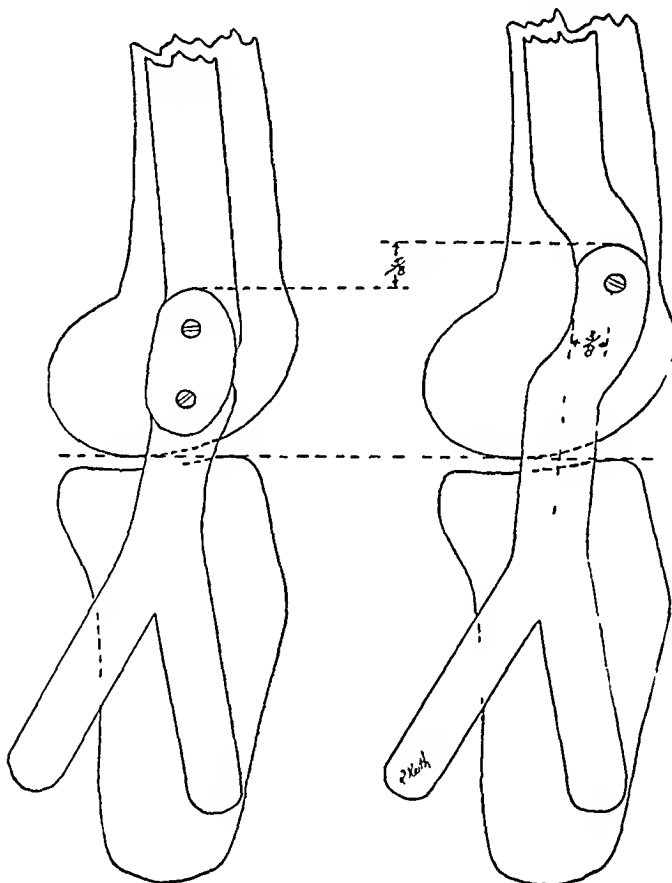


FIG 2

FIG 5

Models were made and, after considerable experimenting, a joint was devised that would fulfill the above requirements. For the purpose of this paper details of the actual joint mechanism are irrelevant. Suffice it to say that it is of a simple hinge variety whose axis is offset  $\frac{3}{8}$  inch anterior to the long axis of the brace. (See Fig 5)

Figure 5 is a tracing of the proposed model joint superimposed on the roentgenogram tracing of the patient's knee. This is the position of the joint during weight-bearing. Compare this with the position of the old prosthetic joint during weight-bearing. For convenience, Figure 2 has been reproduced beside Figure 5. Note in Figure 5 that the joint has been raised  $\frac{5}{8}$  inch, but that the overall length of the brace is the same. Also note the  $\frac{3}{8}$ -inch anterior offset of the prosthetic joint axis.

When there is no weight-bearing on the prosthesis it slides distally 1 5 inches, as explained previously, thus bringing the prosthetic joint down to lie in the desired plane as illustrated in Figure 6 (Compare Figs 5 and 6)

Figure 6 shows the position of the prosthetic joint without weight-bearing when flexion would be desired. It is the same relative position as that of the joint in Figure 7

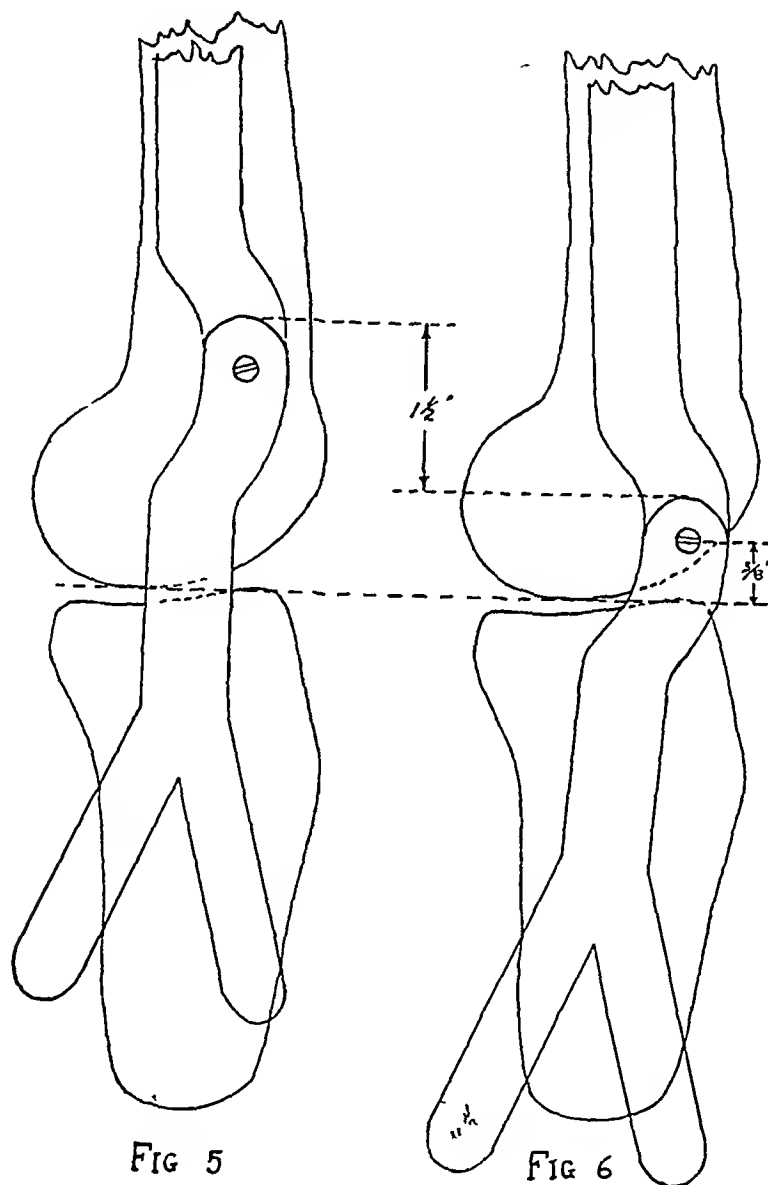


Figure 7 shows the flexed position. Note that the long axis of the prosthesis A-B and that of the stump C-D are parallel. This insures a parallel relationship between the anterior tibial crest and the front of the prosthesis. Thus, when the leg is extended there will be an equal distribution of pressure along a broad area of the tibial crest. See bracket E as compared with the small pressure point E in Figure 1. Now compare Figure 4 and Figure 7 and note that in the latter the prosthesis is held well up on the stump in spite of having to lengthen the lower brace. This is accomplished by the anterior offset of the joint axis.

SUMMARY—1 A case has been presented of a patient with a below-knee amputation who complained of painful pressure on the anterior tip of the stump where it contacted his prosthesis while manipulating the prosthesis in a position of flexion

2 An attempt has been made to illustrate and explain how, in this particular case, the pain was caused

3 A solution to the problem has been presented and illustrated

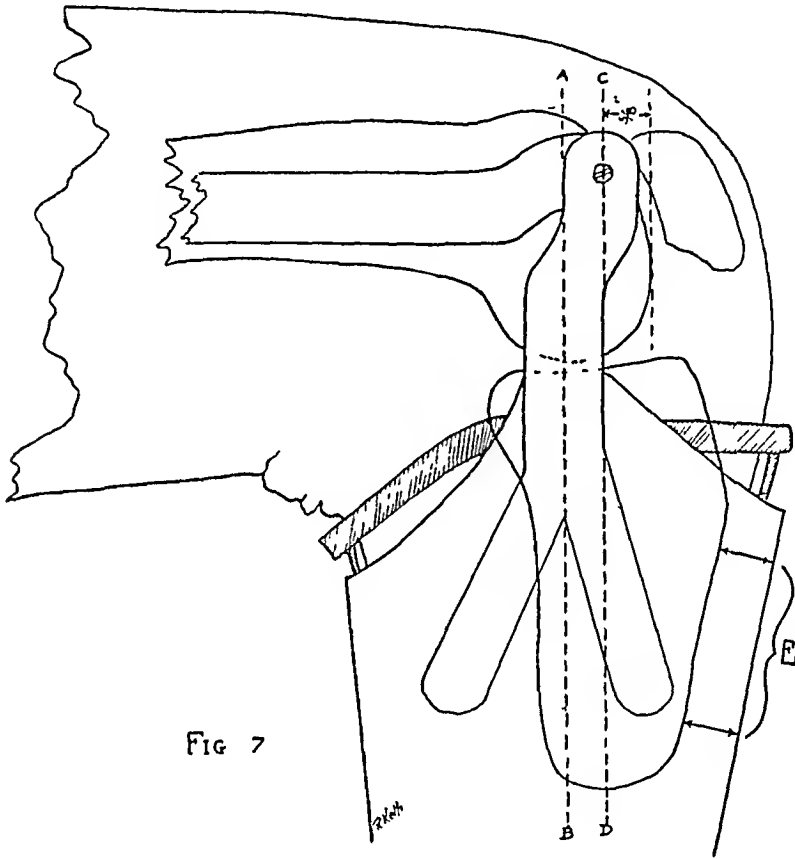


FIG 7

#### CONCLUSION

This is a single case, and further study will be necessary to prove the value of the suggested change in the type of prosthetic joint. The change, however, is based on fundamental principles of mechanics and, therefore, should hold true for all below-knee amputations. In the near future, there will undoubtedly be many below-knee amputations requiring prostheses, and it is also reasonable to presume there will be many complaints registered similar to those of the patient mentioned in this paper. The proposed joint is of a more simple construction, it should be less expensive to manufacture and require less frequent repair subsequent to the original fitting.

# THE RACIAL DISTRIBUTION OF CANCER

## II—TUMORS OF THE KIDNEY, BLADDER AND MALE GENITAL ORGANS<sup>†</sup>

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IN A PREVIOUS COMMUNICATION<sup>7</sup> methods were presented for the analysis of the racial distribution of cancer. The percentage colored (*i e*, the ratio of colored patients to all patients) was determined for each tumor studied, and was compared to the percentage colored for a control group. This group consisted of all patients with cancer except those with certain types of tumors. The work is continued in this study on the racial distribution of tumors of the kidney and bladder in both sexes and of the male genital organs.

*Carcinoma of the Kidney*—According to the data of Hines Hospital (Table I), the percentage colored for carcinoma of the kidney (5.64 per cent of 195 patients) did not deviate appreciably from that of the control group (8.45 per cent of 8,572 men). An analysis of only those cases, which were diagnosed histologically, as transitional carcinoma of the renal pelvis showed approximately the same percentage colored as the control. Similarly, an analysis of the data of the U. S. Public Health Service<sup>1, 2, 3, 4, 6, 8, 9</sup> showed no significant differences in the racial distribution for tumors of the kidney and for the control group (6.49 and 5.61 per cent colored, respectively, for men and 4.76 and 6.83 for women [Table I]). In none of the localities surveyed was there any significant difference between the percentage colored for renal cancer and for the corresponding control. The mortality statistics<sup>5</sup> also showed approximately the same percentage colored for tumors of the kidney (4.57 for men and 4.40 per cent for women) and for the control groups (4.75 and 5.27).

According to the data from the three sources, the racial distribution of cancer of the kidney is the same as that for the control groups.

*Tumors of the Bladder*—Of 430 men with carcinoma of the bladder in Hines Hospital, only 4.88 per cent were colored. This is significantly lower than the 8.45 per cent for the control. Low percentages were also observed for papilloma of the bladder (2.36 per cent of 127 patients).

In surveys of five geographic areas, the U. S. Public Health Service reported 654 male patients with tumor of the bladder. Only 1.98 per cent of the patients were colored. This is significantly lower than the 5.61 per cent colored for the control. In each of the five localities, the percentage

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colored for tumors of the bladder was lower than the corresponding control. According to the mortality statistics, the percentage colored for tumors of the bladder in men (3.72 per cent) is also significantly lower than the control percentage (4.75 per cent).

It seems then that in men tumors of the bladder occur in relatively few colored individuals. In women no significant differences were observed in

TABLE I

THE RACIAL DISTRIBUTION OF TUMORS OF THE GENITO URINARY TRACT ACCORDING TO DATA FROM HINES HOSPITAL, THE SURVEY OF THE U. S. PUBLIC HEALTH SERVICE AND THE U. S. MORTALITY STATISTICS

	Percentage Colored					Number of Individuals All Cases				
	Male		Female			Male		Female		
	Hines Hosp	Public Health Survey	Mortality Statistics	Public Health Survey	Mortality Statistics	Hines Hosp	Public Health Survey	Mortality Statistics	Public Health Survey	Mortality Statistics
Cancer all types	6.29	4.24	4.61	8.32	7.00	11,790	19,615	278,860	24,735	336,844
Benign lesions all types	5.82	—	—	—	—	1,699	—	—	—	—
Control groups										
Cancer	8.45†	5.61†	4.75†	6.83§	5.27§	8,572	14,022	265,993	15,100	256,945
Benign lesions	8.50¶	—	—	—	—	1,106	—	—	—	—
Kidney Cancer	—	6.49	4.57	4.76	4.40	—	231	4,983	126	3,816
Kidney Carcinoma	5.64	—	—	—	—	195	—	—	—	—
Bladder Cancer	—	1.98*	3.72*	5.74	5.70	—	654	13,145	261	5,985
Bladder Carcinoma	4.88*	—	—	—	—	430	—	—	—	—
Bladder Papilloma	2.36*	—	—	—	—	127	—	—	—	—
Prostate Cancer	—	7.58*	4.84	—	—	—	1,490	27,447	—	—
Prostate Carcinoma	11.23*	—	—	—	—	374	—	—	—	—
Penis Carcinoma	27.50*	—	—	—	—	120	—	—	—	—
Other genito urinary sites Cancer	—	—	14.74*	—	—	—	—	1,411	—	—
Scrotum Cancer	—	—	13.71*	—	—	—	—	151	—	—
Scrotum Carcinoma	25	—	—	—	—	8	—	—	—	—
Testis Cancer	—	—	2.60*	—	—	—	—	1,803	—	—
Testis Carcinoma	3.04*	—	—	—	—	263	—	—	—	—

\* The percentage colored is significantly different from that of the corresponding control group.

#### Composition of Control Groups

† All male patients with cancer except those with carcinoma of the exposed skin and lip.

‡ All men with cancer except those with cancer of the skin and lip.

§ All women with cancer except those with cancer of the skin, lip, uterus and cervix.

¶ All male patients with benign lesions except those with keratosis and leukoplakia.

the percentage colored for cancer of the bladder and of the control groups (5.74 and 6.83 per cent, respectively, for the U. S. Public Health Survey and 5.70 and 5.27 per cent for the mortality statistics).

*Carcinoma of the Prostate*—Hines Hospital had 374 men with carcinoma of the prostate, and 11.23 per cent of the patients were colored. This percentage is significantly higher than that of the control group (8.45 per cent).

An analysis of the data of the U. S. Public Health Service gave 7.58 per cent colored of 1,490 men with tumors of the prostate. Although this percentage is greater than the 5.61 per cent colored for the control, the difference is not statistically significant ( $P=0.07$ ). The mortality statistics for tumors of the prostate gave approximately the same percentage colored (4.84 per cent) as the control (4.75 per cent).

The results obtained from the three sources are, for this tumor, not

consistent, and no definite conclusions can be drawn. It is probable that a slightly larger number of colored men develop cancer of the prostate than white men.

*Cancer of the Penis*—Carcinoma of the penis was diagnosed in 120 patients in Hines Hospital. This group of men had the extraordinarily high figure of 27.5 per cent colored, which is considerably and significantly higher than the 8.45 per cent for the control group.

In the mortality statistics, cancer of the penis is included in the category "Other Male Genito-urinary Tumors." The percentage colored for this group of tumors is 14.74 per cent, which is much higher than the control 4.79 per cent.

It is quite definite that an extraordinarily large percentage of patients with tumors of the penis is colored.

*Cancer of the Scrotum*—Scrotal tumors are rare, and only eight cases were observed in the hospital. Of these, two were colored. The mortality statistics record 151 deaths with this tumor, and 13.71 per cent were colored. This percentage is approximately the same as that for tumors of the penis (14.74 per cent), and is significantly higher than the control.

Patients with tumors of the scrotum, then, like those with cancer of the penis, occurred in a relatively large number of colored men.

*Cancer of the Testis*—Hines Hospital had 263 patients with tumor of the testis and, of these, only 3.04 per cent were colored. This percentage is significantly lower than that for the control group.

The mortality statistics gave a percentage colored of 2.60 per cent as compared to a control of 4.75 per cent. Further analysis of the data showed that in the older age-groups (50 years or over) the percentage colored for tumors of the testis is approximately the same as the corresponding control. It seems that young patients with tumor of the testis have a relatively low percentage colored, whereas older men with this tumor have the same percentage colored as the control group. The findings suggest that testicular cancer occurred less frequently in young Negroes than in young white men, but in older individuals the tumor was equally common in the two races.

**DISCUSSION**—Surprisingly good agreement on the racial distribution of patients with genito-urinary tumors was obtained by analyses of the statistics from three diverse sources, namely, (1) patients of Edward Hines Jr. Memorial Hospital, (2) the survey on cancer by the Public Health Service, and (3) the mortality statistics of the United States. This agreement suggests that the observations are significant both statistically and biologically.

It was noted that patients with tumors of the penis and scrotum had a relatively high percentage colored and those with cancer of the prostate had possibly a slightly higher percentage colored than the control groups. On the other hand, men with neoplasms of the bladder and testis had low percentages colored. Cancer of the kidney in men and women and cancer of the bladder in women had approximately the same racial distribution as the control groups.

The observed high percentage colored in patients with cancer of the penis and scrotum may be attributed to extrinsic environmental factors, such as local unhygienic conditions and chronic inflammatory processes. The biologic factors responsible for the low percentage colored for cancer of the bladder and testis are not evident. It is even hazardous to guess whether extrinsic environmental factors or intrinsic racial differences in susceptibility are involved.

#### SUMMARY

The incidence of cancer of the genito-urinary tract in the white and colored race was studied indirectly by the method of determining the percentage colored for the tumor and for a control group.

According to this method, cancer of the penis and scrotum and possibly cancer of the prostate occurred relatively more frequently in colored than in white men. Colored men below age 50 had a relatively low incidence of cancer of the testis, but Negroes above age 50 had the same incidence of this tumor as white men. Colored men but not colored women had a relatively low incidence of cancer of the bladder. Tumors of the kidney occurred equally frequently in white and colored individuals.

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# BRIEF COMMUNICATION

## AN UNUSUAL CASE OF PENETRATING FOREIGN BODY IN THE MEDIASTINUM

### CASE REPORT

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THE FOLLOWING CASE IS presented because of its unusual nature with respect to the type of foreign body, the mode of introduction into the mediastinum, the absence of serious injury to vital structures, and the interesting surgical problem presented in its removal

**Case Report**—New Haven Hospital No B-48156 M V, white, female, age 57, was admitted to the Surgical Service October 21, 1943. For several weeks she had been in a psychiatric hospital, with a diagnosis of manic-depressive psychosis. On the day of admission, she managed to secrete a straight steel crochet hook on her person. About two hours before admission, with suicidal intent, she forced the crochet hook through the skin of the jugular notch until it was lost in the depth of the tissues. After a brief period of remorse, she informed a nurse of her action. In view of the patient's good physical condition and the absence of any significant external wound, the nurse was inclined to discredit the patient's story, but wisely called the physician in charge who ordered roentgenograms of the chest (Figs 1 and 2). This revealed the crochet hook lying in the mediastinum and bent at an angle of 45 degrees. The patient was immediately transferred to the Thoracic Service.

**Physical Examination**—The patient appeared as an hyperkinetic, slightly disoriented, elderly white female in apparently good physical condition. She complained only of slight pain in the posterior thoracic midline and reiterated her desire to die. Pulse 72, the rhythm regular, blood pressure 172/94. There was a pinpoint, dry wound in the jugular notch, no foreign body could be felt under it. There was no evidence of cyanosis, no subcutaneous emphysema of neck or chest, no dyspnea, and only moderate hyperpnea (respirations 38). The lung fields were clear to percussion and auscultation, there was no pleural or pericardial friction rub. The abdomen was negative to palpation. The pulses of the lower extremities were full and equal, the femoral blood pressures were equal bilaterally.

**Operation**—Approximately one hour after admission, anesthesia was induced with nitrous oxide and cyclopropane, the trachea was intubated, and insufflation of ether-oxygen mixtures begun. With the patient in the supine position, the entire anterior and lateral chest including the lower neck was prepared and draped. A submammary incision was made on the left and, after elevating a flap of breast and pectoral muscles, the anterior half of the fourth rib and cartilage was resected. On opening the left pleural cavity, there was no evidence of preëxisting pneumothorax or bloody effusion, the mediastinal pleura appeared quite normal, there was no emphysema. The mediastinal pleura was opened just behind the phrenic nerve above the pulmonary hilus, uncovering the pulmonary artery, which was uninjured. The foreign body could not be felt. The lung was then retracted forward and the posterior mediastinal pleura incised. Behind the proximal portion of the left primary bronchus the end of the

hook was quickly exposed. It was cut off with a heavy shears. The shaft of the hook was then easily manipulated into the pleural cavity and removed (Fig 3). The mediastinal pleural defect was allowed to remain open for drainage and the chest closed in layers, with silk, reexpanding the lung with slight positive pressure and by aspiration of the residual pneumothorax. About 5 Gm of sulfathiazole powder was dusted into the mediastinal area and pleural cavity during closure. Operation time 90 minutes.

Convalescence was uneventful. The patient received sulfadiazine therapy for eight days, at which time she was afebrile and ambulatory. The wound healed *per primam*, the left lung expanded well without significant pleural effusion, and she was discharged to the Psychiatric Service on the ninth postoperative day.

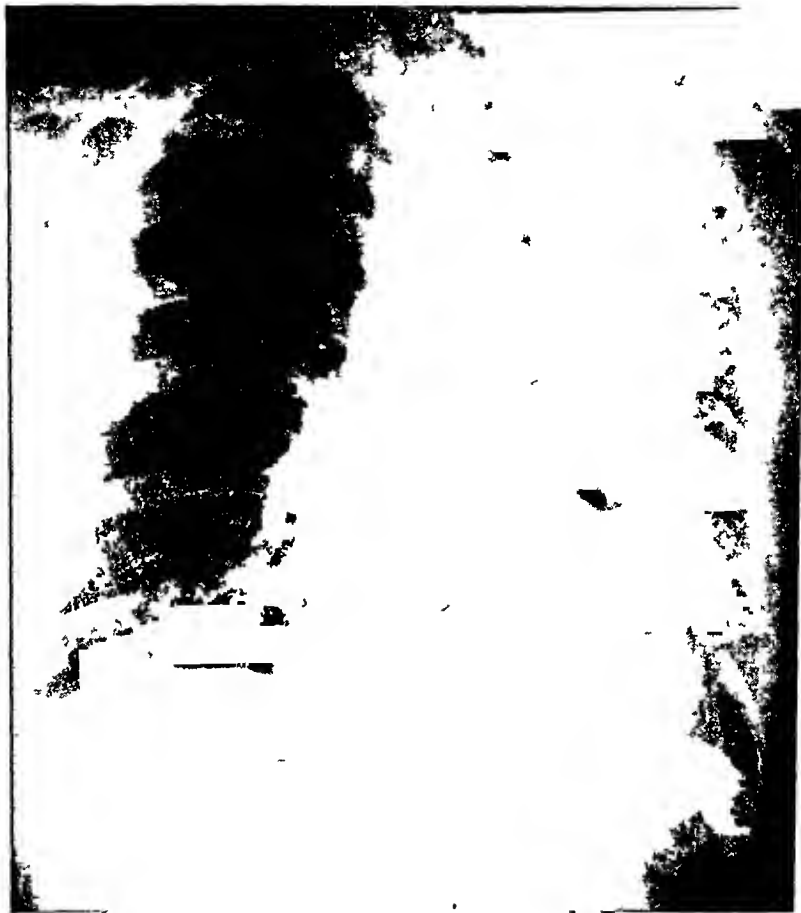


FIG 1—Preoperative postero anterior roentgenogram of chest

DISCUSSION—The possible treatment of this patient's surgical problem presented several alternatives

1 Conservative or nonoperative management with chemotherapy in an attempt to control possible mediastinitis. In favor of this course was the mental status of the patient. Against it was the high probability of secondary pressure erosion of a large vessel or the esophagus.

2 Surgical removal of the hook, by retrograde extraction in the jugular notch under local anesthesia. In favor of this procedure was its apparent

simplicity and the avoidance of major thoracotomy. Against this procedure were the fact that the needle could not be palpated in the neck, its evident angulation, and the presence of a hooked end which could easily produce a tear of vital structures during withdrawal. Furthermore, this route would not give the opportunity to examine directly for complications in the mediastinum and to attempt their control, if found to be present.



FIG. 2—Preoperative lateral roentgenogram of chest.

3. Transthoracic mediastinotomy. This was the procedure of choice, in view of the considerations mentioned above.

It is interesting to speculate on the probable course of this foreign body as it entered the superior mediastinum, in order to explain its final location and its failure to penetrate the trachea, esophagus or large vessels. Having been introduced by a right-handed person, it doubtlessly inclined slightly downward and to the left, slipped above the left innominate vein, grazed the

trachea, slid over the arch of the aorta between the innominate artery and the left internal carotid, and missed the left border of the esophagus. Impinging on a vertebral body, a second hard push (as described by the patient) angulated it. Its point then passed inferiorly to rest behind the left pulmonary artery and left primary bronchus, in which position it was discovered at operation.

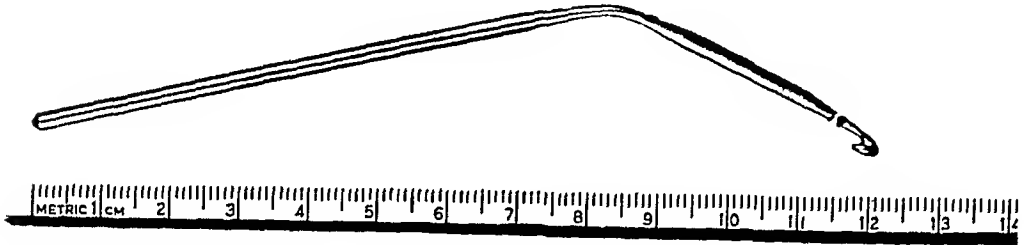


FIG 3.—Photograph of the foreign body, showing point of section and angulation of the shaft

#### SUMMARY

An unusual case of penetrating mediastinal foreign body (steel crochet hook) is presented. The considerations determining the method of removal and the probable anatomic course of the penetration are discussed.

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## WOUNDS OF THE HEART

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IN NOVEMBER, 1940, I made a report concerning 38 patients who had been operated upon for wounds of the heart or intrapericardial portions of great vessels<sup>1</sup>. All of these patients were operated upon in the Emory University Division of Grady Hospital, Atlanta. Since that time 23 patients have been operated upon in the same clinic for similar conditions, and these latter cases are here reported in abstract, with further observations upon this condition particularly as regards its treatment.

With the exception of Case 1 the patients in this latter series were operated upon by members of the Resident Staff, and to them should go full credit for the continued interest in this field of traumatic surgery. Of these 23 patients there were five deaths, a mortality of 22 per cent, whereas, in the previously reported 38 patients 16 died, a mortality of 42 per cent—a combined mortality in the 61 patients of 34 per cent. It is believed that this reduction in death rate was due to several factors. The resident surgeons who performed these operations have gone through a period of graduated preparatory training during which time they are allowed to assist in and perform procedures of this type on their own responsibility and, as a result, become more skillful in the performance of such operations. Moreover, they are constantly on the alert to make a proper diagnosis and in proceeding with treatment with the least possible delay.

In the first series seven deaths were recorded as due to infection, pericarditis, pneumonia, and bacteremia. In the latter series there were no deaths from infection, and those patients who did not recover either died on the operating table, or shortly thereafter, presumably from hemorrhage or from the effects of tamponade. The reduction in mortality from infection was not due to the use of sulfa drugs since in the second series it was only used in one case (Case 1) for the treatment of postoperative pneumonia. In no instance has it been placed in the wound. I believe that the reduction in infections is, in the main, due to a more meticulous technic and in careful preoperative preparation. In no instance of the latter series has careful preparation and operative technic been sacrificed for speed and haste.

Another factor which may be of considerable importance has been the giving of intravenous fluid prior to operation. I was formerly of the opinion, which was largely based upon the work of Beck,<sup>2</sup> that *in the presence of*



*tamponade*, the giving of blood or any other fluid intravenously was of no value since the tamponade would prevent its reaching the heart. The experimental work of Cooper, Stead, and Waiien<sup>3</sup> presents evidence that the rapid intravenous infusion, with subsequent increase in blood volume, enables a dog to withstand a considerably higher intrapericardial pressure. Based upon this conclusion, intravenous infusions were given to the last eight patients, and in each there was a clinical improvement preoperatively.

All the patients in this series, as well as those previously reported, were operated upon since in each there was definite evidence of cardiac tamponade. This diagnosis was based upon the lowered arterial pressure and increased venous pressure, and the presence of a quiet heart as noted on fluoroscopic examination. This latter diagnostic point was first described by Bigger,<sup>4</sup> and has since been emphasized by others. Of all signs leading to a diagnosis of tamponade this is the most important and is the one least likely to lead to a mistaken diagnosis.

Venous pressure readings are not only of value in the diagnosis of tamponade but are of considerable prognostic importance. If the venous pressure is high, that, in itself, is evidence that the heart is carrying on its functions and that the cardiac output is at least sufficient to produce such pressure. On the other hand, a low or lowered venous pressure in the presence of tamponade is evidence of a failing heart and of a greatly reduced cardiac output. In this connection, it is interesting to note that Case 9, with a venous pressure of 120 mm of water, died two hours after operation, that Case 16, with venous pressure of 150 mm of water, died on the table, and that Case 21, with venous pressure of 210 mm of water, died on the table.

It will be noted that in all patients there was a definite lowering of the arterial pressure, and in 17 of the 23 blood pressure readings could not be recorded. In those patients who recovered there was an immediate rise in arterial pressure following the release of the tamponade.

Some type of general anesthesia in which positive pressure can be used for inflation of the lung is preferable to local anesthesia. The difficulties of heart suture require that the patient be quiet, and these patients are usually excited or may become so with the release of the tamponade and, unless completely anesthetized, their movements may interfere with the operation at the most inopportune time.

As previously pointed out, the approach to the heart is made on the left side of the sternum with the incision placed about one intercostal space below the external wound. In most instances a transverse incision extending from about two centimeters outside the nipple line and carried well across the sternum has been used. By this approach one or two ribs can be removed, and, if necessary, the adjacent costal cartilages cut and a portion of the sternum removed. The pectoralis major muscle is separated in the direction of its fibers and can be retracted from the surface of the three ribs. Every care should be taken to prevent opening the pleura since such a complication adds materially to the shock which the patient has already undergone. The

WOUNDS OF THE HEART

TABLE I  
SUMMARY OF 23 CASES OF CARDIAC WOUNDS

No	Operator*	Sex	Age	Instrument	Duration from Injury to Operation	H2O Venous Pressure	Arterial Pressure		Tamponade	Location	Complications	Amount of Blood Given	Result
							Pressure on	Pressure after					
1	D C E	F	27	Ice pick	80 mins	250 mm	0/0	110/70	+	R auricle	Pneumonia	750 cc	Recovery
2	C S W	M	33	Knife	60 mins	200 mm	60/40	120/80	+	R ventricle	L hemothorax	300 cc	Recovery
3	C S W	M	27	Knife	60 mins	220 mm	80/55	130/70	+	Pul conus	I hemothorax	500 cc	Recovery
4	C S W	M	28	Knife	60 mins	270 mm	0/0	110/80	+	R ventricle	L hemothorax	1000 cc	Recovery
5	W C W	M	25	Knife	60 mins	230 mm	50/35	120/70	+	Pul conus	L hemothorax	600 cc	Recovery
6	R F M	F	31	Knife	75 mins	190 mm	0/0	110/80	+	I ventricle	None	600 cc	Recovery
7	R F M	M	23	Ice pick	90 mins	210 mm	0/0	100/50	+	L ventricle	None	600 cc	Recovery
8	F W C	M	28	Knife	40 mins	190 mm	0/0	100/60	+	R ventricle (int and post)	R hemothorax Pneumonia	1000 cc	Recovery
9	F W C	M	40	Knife	90 mins	120 mm	0/0	110/70	+	Pul artery	Died	1000 cc	Died—2 hrs
10	W C W	F	19	Knife	90 mins	200 mm	0/0	0/0	+	R ventricle	Died	800 cc	Died—2 hrs
11	W C W	M	24	Knife	90 mins	160 mm	0/0	110/70	+	R ventricle	R hemothorax	1000 cc	Recovery
12	W C W	M	18	Knife	80 mins	110 mm	50/0	100/80	+	R ventricle	I hemothorax	1000 cc	Recovery
13	F W C	M	41	Knife	60 mins	250 mm	0/0	160/80	+	L ventricle	L hemothorax	1000 cc	Recovery
14	C M H	M	26	Knife	15 mins	190 mm	0/0	0/0	+	Pul artery	Died	500 cc	Died—10 mins
15	W C W	M	22	Knife	120 mins	180 mm	0/0	160/60	+	R ventricle	None	600 cc	Recovery
16	W C W	M	27	Knife	90 mins	150 mm	0/0	0/0	+	L auricle	Died	1000 cc	Died on table
17	C M H	M	44	Knife	60 mins	190 mm	80/50	110/70	+	Aorta	None	1500 cc	Recovery
18	W H P	M	43	Knife	60 mins	210 mm	0/0	120/70	+	R auricle	L hemothorax	1500 cc	Recovery
19	C M H	M	36	Knife	60 mins	200 mm	70/40	130/70	+	R ventricle	Pericardial effusion	1500 cc	Recovery
20	W H P	M	29	Knife	60 mins	190 mm	0/0	120/70	+	Pul artery (2 openings)	I hemothorax	2000 cc	Recovery
21	W H P	F	33	Knife	120 mins	120 mm	0/0	0/0	+	Undetermined	Died	1000 cc	Died on table
22	W H P	M	52	Ice pick	120 mins	210 mm	0/0	120/60	+	Pul artery	L hemothorax	1500 cc	Recovery
23	W H P	M	50	Knife	90 mins	220 mm	0/0	110/70	+	Pul conus	Pneumonia	1000 cc	Recovery

\* The operating surgeons referred to by initial in the summary of these cases were Doctors Charles S Ward W Cleve Ward Robert F Mabon F W Cooper and Wm H Proctor

internal mammary vessels must be carefully isolated and ligated. They may not bleed before the tamponade is released, but later hemorrhage from them may be fatal unless proper ligation has been performed. The pleura on the left is displaced from the pericardium by gauze dissection and held out of the wound by a wet pack. As a rule, the pericardium will be tense, and its pulsations weak or imperceptible. If the wound in the pericardium is seen it should be enlarged or, if not readily found, it is opened between stay-sutures. Occasionally the heart wound can be located before the blood and clots are removed and before the heart starts beating actively, and under such conditions it can be readily sutured. More often the heart wound is not disclosed until blood and clots are removed by suction. When the intrapericardial pressure is relieved the bleeding becomes marked and contractions of the heart increase in force. When the wound is located, and it is most often found in the right ventricle, its closure is facilitated by placing the left index finger over it. In this way the bleeding will be impeded sufficiently to allow the passage of a suture directly under the finger. This is left untied for the moment and is held in the left hand for traction hemostasis while other sutures are placed and tied. Should the wound be behind the sternum or on the posterior surface of the heart a stay-suture passed through the apex, as advocated by Beck,<sup>5</sup> is of great value. By this means the wound may be rotated into a favorable position for suture. It is to be noted that there were two instances of double wounds, one of the pulmonary artery with recovery, and one in the anterior and posterior surface of the right ventricle, which recovered. In this second case the use of the apex stay-suture was of particular value in rotating the heart into a position where the posterior wound could be successfully sutured. Wounds of the coronary vessels may require ligation but are not necessarily fatal. Beck<sup>2</sup> has recently devised an ingenious method of suturing wounds in the vicinity of the coronary vessels without injuring them. The pericardium should be closed loosely to allow the escape of pericardial fluid, but the chest wall should be sutured with careful approximation of the anatomic layers. Details concerning the suture of wounds of the auricles and great vessels have been previously described.<sup>1</sup>

The opinion was expressed by me in a previous paper<sup>1</sup> that operation should be carried out as soon as the diagnosis of a heart wound is established. In view of the reports from other clinics on this subject this opinion should probably be modified to include some form of conservative treatment if conditions are not urgent and operation does not seem to be immediately demanded. Bigger,<sup>6</sup> Strieder,<sup>7</sup> and Blalock<sup>8</sup> have emphasized the value of aspiration of the pericardium as a preliminary to operation, and in some instances it has been found that aspiration alone is the only operative procedure necessary, since some wounds, particularly those which do not penetrate the cavities of the heart, have sealed, and aspiration of the blood relieving the tamponade is sufficient to bring about a cure. Blalock<sup>8</sup> advocates that in cases of tamponade where there is no bleeding into the chest or to the

outside, that the pericardium be aspirated, but that "all facilities should be available for immediate operation if it becomes necessary" He further states that "if blood reaccumulates rapidly following aspiration, it is agreed that exposure and suture of the heart wound is indicated" He also makes a statement that "if one has good reason to believe that an auricle rather than a ventricle has been injured, one may more safely defer operation" I do not believe there is any method whereby it may be determined whether an auricle, a ventricle, or the intrapericardial portion of a great vessel is the point of injury The direction of the knife-thrust or a bullet wound is notoriously misleading, and the position of the cardiac wound cannot be determined by the wound of entrance, and the symptoms of tamponade are the same no matter what the source of the bleeding It would seem then that the only modification of the advocacy of immediate suture would be continued improvement following aspiration without recurrence of the signs of cardiac compression

#### CONCLUSIONS

Twenty-three patients operated upon for wounds of the heart are presented in abstract These are in addition to 38 cases of similar nature previously reported from the Department of Surgery, Emory University, Grady Hospital, Atlanta The mortality rate in the latter series was 22 per cent as compared with 42 per cent in the first series

Conjectured reasons for this lower mortality rate are presented

It is believed that the giving of intravenous infusions prior to operation has a beneficial effect by increasing blood volume and, hence, cardiac output

While immediate operation was undertaken in all patients of this series, and carried out as soon as diagnosis was made, it appears evident from the reported cases of other clinics that aspiration of the pericardium, both as a temporary and definitive method of treating cardiac tamponade may be properly employed Operation should not be delayed if there is evidence of bleeding into the pleural cavity or through the external opening

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# THE BENEFICIAL EFFECT OF INTRAVENOUS INFUSIONS IN ACUTE PERICARDIAL TAMPONADE\*

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ALTHOUGH STAB WOUNDS of the heart with pericardial tamponade are not common, they do constitute a unique and serious problem in emergency therapy. These patients usually arrive at the hospital in profound shock, with coma, cold, clammy extremities, unobtainable arterial pressure, and distended veins. Knowledge of the circulatory dynamics is not only of considerable theoretic interest, but of practical importance in therapy as well. It is obvious that the circulation can be maintained only as long as the venous pressure exceeds the elevated intrapericardial pressure. It was felt that a consideration of the factors leading to elevation of the venous pressure might lead to a more rational basis for therapy.

The elevated venous pressure in pericardial tamponade is usually said to be produced by damming up of blood behind the obstruction to the venous inflow to the heart, much as a dam causes a stream to fill up and form a lake. Such an analogy is applicable to the increase in venous pressure which is produced in an extremity by blocking the venous outflow with a tourniquet. The retained blood fills and distends the veins of the part until the pressure within them can overcome the block. At this point the veins of the extremity contain more blood than before, this blood being obtained by compensatory vasoconstriction in other parts of the body. By this method the venous pressure in a part can be elevated practically to the level of the systolic arterial pressure. It must be remembered that the lake is formed not with the water that is continually being added to the stream from above. Thus, the analogy of the dammed stream in its entirety is not applicable in pericardial tamponade, because the circulation is a closed system in which the venous inflow to the heart is dependent upon the cardiac output. The amount of venous distention which can be caused by damming up the venous inflow to the heart is limited by the fact that a decrease in cardiac output rapidly diminishes the stream of blood entering the venous system. The venous pressure must be raised in some manner by the use of blood already in the vascular bed and not by blood being constantly fed into it from fresh sources. Blood in small amount is obtained by vasoconstriction forcing blood in peripheral vascular beds into the larger veins. With the fall in arterial pressure less blood is contained in the arterial tree, and this blood also becomes avail-

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\* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Emory University School of Medicine

able to fill and distend the venous system. Thus, the rise in venous pressure is produced by a combination of vasoconstriction and redistribution of blood in the vascular bed. It must be remembered that most patients with stab wounds of the heart have lost blood externally, so that the vasoconstrictor mechanisms have already been called into play to compensate for the decrease in blood volume. Under these conditions the body is at a disadvantage in attempting to raise the venous pressure to overcome the tamponade.

Another method by which the venous pressure may be elevated is an increase in blood volume. This is an important mechanism in the elevation of the venous pressure in chronic congestive heart failure, but does not operate in acute pericardial tamponade because the onset is almost instantaneous. The capillary pressure throughout the body is elevated, so that rapid passage of fluid into the blood stream does not occur. Since survival in pericardial tamponade is dependent upon elevation of the venous pressure, it appeared that the use of intravenous fluids to raise the venous pressure by increasing the blood volume might be beneficial. The following experiments were undertaken to test such an hypothesis.

*Methods*—Medium-sized dogs were used, two of which were subject to splenectomy two weeks prior to the experimental procedure. Under sodium pentobarbital anesthesia, and with positive pressure artificial respiration, the left pleural space was opened and the pericardium exposed. A flanged metal tube, similar to that used by Katz and Gauchet,<sup>1</sup> was inserted into the pericardium and screwed down to form a water-tight junction. A small rubber tube attached to the metal one traversed the dorsal portion of the left chest. The wound was closed tightly about the rubber tube and the air remaining in the pleural space was aspirated.

Several hours later the experiments were conducted. At this time the animals breathed naturally, without difficulty, and were alert and active. The rubber tube was connected with a reservoir of physiologic saline solution so that the intrapericardial pressure could be varied at will. A No. 8 ureteral catheter was inserted in the superior vena cava and the central venous pressure measured directly in centimeters of water. The mean arterial pressure was obtained in some experiments by direct femoral puncture. At the conclusion of the experiment, the operative site was examined to check the position and function of the tube in the pericardium.

*Results*—Experiments were carried out upon five dogs. In all, rapid elevation of the pericardial pressure produced similar results. As the saline reservoir was raised, the venous pressure rose concomitantly, remaining slightly above the intrapericardial pressure. The arterial pulse became paradoxical in quality and finally was imperceptible. As the pressure was increased the respirations became irregular and gasping, then ceased, usually with the heart still beating. If the pressure was released at this time, the respirations would usually resume, although at times artificial respiration would be necessary for a few minutes. The response of the splenectomized dogs appeared no different from those with the spleen intact.

The pressure required to produce such symptoms was quite constant for a given dog, but varied considerably from animal to animal. It ranged from 12 to 22 cm of  $H_2O$  pressure. After determination of the pressure required to produce such severe symptoms, a rapid intravenous infusion of physiologic saline solution was given to temporarily increase the blood volume. That it did so was demonstrated by a fall in hematocrit reading and plasma protein concentration. Several minutes after infusion was started the ability of the dog to withstand increased pericardial pressure was retested. In three such experiments the dog withstood 92, 95, and 146 per cent greater pressure than previously. In two instances after the blood volume had returned to normal, the ability to withstand increased pericardial pressure had diminished and the entire procedure was repeated, with similar results.

In human cases of pericardial tamponade the situation is slightly different, in that the tamponade is already present when therapy is started and the rent in the pericardial sac is usually closed. Therefore, two experiments were conducted with a closed system. Severe tamponade was produced and the lumen of the rubber tube leading from the pericardium was then occluded. In both of these dogs there was distinct improvement with the administration of approximately 300 cc of saline solution. In the one instance the mean arterial pressure rose from 40 Mm Hg to 78 Mm Hg. The intrapericardial pressure and venous pressure as measured after improvement rose less than two centimeters of water.

COMMENT—The pressure in the pericardium necessary to produce circulatory failure in our dogs was similar to that previously reported.<sup>1</sup> The effects of saline infusion are similar to those reported by Beck,<sup>2</sup> except that he was unable to obtain improvement when the tube leading to the pericardium was clamped off. From a theoretic standpoint, it appears that improvement in the circulation under these circumstances would depend upon the ability of the pericardium to stretch and allow an adequate cardiac filling with the increased venous pressure. In our dogs such stretching appeared to occur, and the increased pericardial pressure was more than compensated by the increased venous pressure.

The physiologic alterations in acute pericardial tamponade are not similar to those in chronic constrictive pericarditis. In the latter condition cardiac filling is prevented by dense fibrous tissue no matter how high the venous pressure becomes. In acute pericardial tamponade filling can occur if the venous pressure sufficiently exceeds the intrapericardial pressure and if the pericardium is able to stretch.

Opinions differ as to whether the intravenous administration of physiologic saline solution is beneficial in patients with acute pericardial tamponade resulting from a stab wound of the heart or great vessels. In the patients who survive until they reach the hospital the myocardial, and probably the pericardial, rents are at least temporarily closed. Bigger<sup>3</sup> states that intravenous infusions are useful. Elkin,<sup>4</sup> and Griswold and Maguire<sup>5</sup> believe that they are of little benefit. Stimulated by the favorable results in experi-

ments on the dogs, saline infusions have been administered to the last three patients admitted to Grady Hospital with traumatic pericardial tamponade. In each case the arterial pressure rose and the patients became more rational. At operation, the wounds in the heart and pericardium were found to have remained sealed, in spite of the rise in arterial pressure.

Blalock and Ravitch<sup>6</sup> have recently emphasized that the tamponade can frequently be relieved by aspirating the pericardium. They stressed the fact that in many instances the bleeding does not recur and that operation is not necessary. The results reported here suggest that the circulatory failure in acute pericardial tamponade is helped by the use of intravenous infusions. This form of therapy serves as a useful adjunct to the treatment either by aspiration or by operation. It is possible that, in certain selected patients, raising the venous pressure by increasing the blood volume will restore the circulation to an adequate level without either aspiration or operation.

#### SUMMARY AND CONCLUSION

1 Acute pericardial tamponade was produced in dogs. The pressure required to produce severe symptoms varied from 12 to 22 cm of water.

2 A rapid intravenous infusion, with subsequent increase in blood volume, enabled the dogs to withstand 92 to 146 per cent greater pressure.

3 In two dogs severe tamponade was produced, and intravenous saline solution caused striking improvement, even though the pericardium was closed and no fluid escaped.

4 Preliminary observations upon patients with acute pericardial tamponade from stab wounds of the heart indicate that the preoperative administration of intravenous fluids is beneficial.

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# SYNOVIAL SARCOMA

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A NUMBER OF INTERESTING STUDIES of the rare and highly specialized tumor-form, known most commonly as synovial sarcoma, have appeared in recent years. One might expect that a clear conception of the pathology, degree of malignancy, clinical course and results of treatment could be gained by a perusal of these papers. It is distressing to find that this is not so, chiefly because a very considerable number of cases have been reported as synovial sarcomas which were not such, but, in reality, xanthomatous giant cell tumors, tumor-like hyperplasias of the synovial tissues or other benign lesions curable by simple excision. Thus, the apparent cure rate has been made higher than is in fact the truth. It has seemed timely, therefore, to undertake a new study in order to obtain more accurate information.

The procedure has been first to obtain confirmation of the mesothelial nature of the neoplasm by making tissue culture studies of three cases (Nos 98, 99 and 101). This work is reported elsewhere (Murray, Stout and Pogogeff, *ANNALS OF SURGERY*, p 843, this issue), and leaves no doubt about the specialized characteristics of the tumor cells. The three tumors from which these cultures were obtained all had very striking histologic characteristics. They were composed of an inextricable admixture of mesothelial cells which often lined slits or tubes and secreted a mucicarmophilic substance, with strands of active, hyperchromatic fibrosarcoma-like cells associated with reticulin fibers. The relative amounts of these two cell-forms varied enormously, but both of them were always present. It was determined to regard these as the histologic features characterizing this tumor.

With this in mind, cases reported as synovioma, synovial sarcoma, or by some related term, were reexamined and those which did not fulfill our criteria were rejected. This screening yielded 95 cases, to which we add nine additional previously unreported examples, four of them from the Presbyterian Hospital and five from other sources.

An evaluation of the information gleaned from this critically selected group has yielded information of clinical value. Males preponderate in the proportion of 3:2 (males 62, females 41, sex unknown 1). Reference to Chart 1 will show that although this tumor may develop at any age, it is much more frequently found in early adult life than at any other time. The mean age of the 103 patients whose age is known was 32 years.

As is the fact with many bone and joint lesions, synovial sarcomas develop most frequently in the region of the knee joint—nearly half of the tumors have been found in that region. The distribution is as follows. Lower extremity

82 (79 per cent) cases (hip 2, groin 2, buttock 1, thigh 7, knee 49, lower leg 1, ankle 9, foot 10, great toe 1), upper extremity 22 (21 per cent), (axilla 1, elbow 9, forearm 1, wrist 4, hand 3, fingers 4)

It should be pointed out that, whereas, these tumors are composed almost certainly of mesothelial cells, it is very questionable whether or not they are derived from the normal lining cells of joints, tendon sheaths, and bursae, because the tumors are usually outside of these structures although often in close proximity to them. Even when the tumors grow to a relatively large size, it is very rare for the actual lining of joint or tendon sheath to be

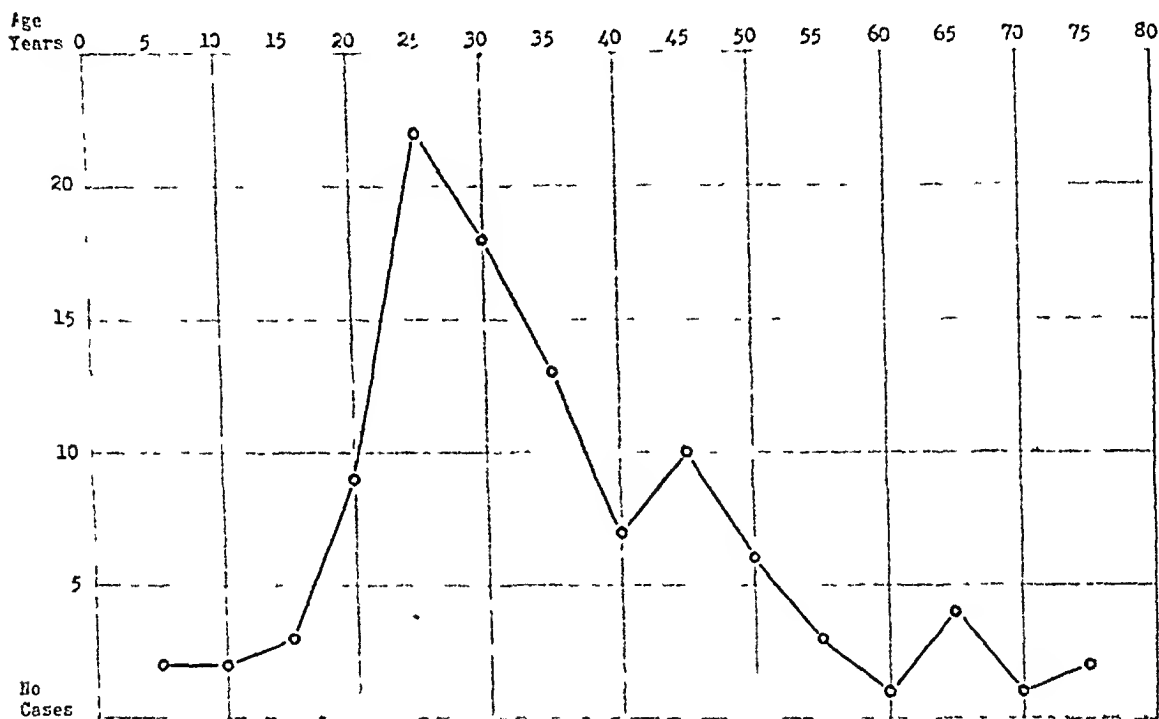


CHART I

Quinquennial Age Distribution of Synovial Sarcomas

affected. Thus, among Briggs' (1942) nine cases only one (Case 88 of this series) involved the synovia, and in our own group of nine cases only one (Case 101) actually involved a synovial membrane. In contradistinction to this, the synovial hyperplasias, giant cell tumors, hemangiomas and other nonmalignant lesions almost always involve the synovial tissues themselves.

The initial symptom of the synovial sarcoma is usually pain. According to Lazarus and Marks (1943) this is preceded in about 25 per cent of cases by a history of trauma. They felt that this was too small to have any etiologic significance, and with this we agree. The pain is often present for a long time, sometimes for several years, before a tumor is noted. The symptoms are so chronic that in a number of these patients the knee has been explored with the provisional diagnosis of internal derangement of the joint. In others the lesion has been mistaken for tuberculosis or for some form of arthritis. The mean duration of symptoms when the patient came for treatment in the 98 cases in which this information was available, was 2.6 years.

The total duration of the disease is correspondingly prolonged. Forty-seven of the patients are known to have died, and in 42 the total duration of disease from the onset of the first symptom to death is stated. It varied from five months to 16 years, the mean total duration being 5.7 years. Only three patients in the group of 104 have been clinically cured for more than five years after treatment. These are cases 33, 83, and 97, which were reported without evidence of tumor six, seven and eight years, respectively. The duration of the disease in the clinically cured cases does not, therefore, influence to any appreciable degree the conclusion derived from the fatal cases that synovial sarcoma is among the more slowly growing of the malignant neoplasms.

Although the disease apparently remains localized for several years, metastases eventually manifest themselves in the great majority of cases. Even though the follow-up data are often incomplete in this collection of cases, metastases were recognized in 43 of the 47 patients who died, while seven others who were still alive also had them. The distribution in these 50 patients suggests that although the blood stream is the usual route for metastases, they are occasionally carried *via* the lymphatics to the regional nodes. The recorded sites of involvement were: Lungs 43, lymph nodes 12 (inguinal 7, axillary 4, iliac 1), skin 2, abdomen 1, bones 1, brain 1, generalized 2.

*Gross Pathology*—The morphologic characteristics of these tumors are quite uniform. Starting from a focal point they grow chiefly by expansion so that they are circumscribed but as they also infiltrate there is no true capsule and they are more or less adherent to surrounding structures. The gross tumor is nodular and is moulded by the density and resistance of the tissues within which it grows. Its firmness depends upon the relative content of its fibrosarcomatous element, whether or not there is calcification or ossification, and upon the amount of degeneration. When cut open the exposed tumor tissue is basically a very pale creamy-pink like the majority of sarcomas but this is generally mottled with reds and yellows from hemorrhage and degeneration. Some of the tumors are quite hard in places where fibrosis and calcification has occurred. They are generally found close to, or adherent to, a joint, tendon sheath or bursa, but it is seldom that they project into the synovial cavity and some tumors, particularly those arising in the thigh, do not appear to be demonstrably connected with any of these structures.

*Histopathology*—The synovial sarcomas are always compounded of two elements both of which are neoplastic and as inseparable as the lining cells of joint, tendon sheath or bursa and the supportive tissue upon which these cells rest. These two may be designated as the fibrosarcomatous element and the synovial element. If one studies a number of different tumors as well as many parts of the same tumor, it becomes apparent that there are almost infinite variations not only in the relative proportions of the two elements with respect to one another but also in the degree of differentiation of the two types.

of tissue in the same and different tumors. Always, however, both types are present in some part of the tumor, inextricably intermingled one with the other. One can best study these tumors by using some silver connective tissue fiber stain because of a basic difference between the two tissue types. The fibrosarcomatous elements are always furnished with reticulin fibers which will be blackened by the silver while the synovial elements are always free from fibers. Thus, with a silver stain the relative proportions of the two elements are distinguishable at a glance no matter what the stage of differentiation. Both cell types are found in a number of different guises with varying degrees of differentiation.

The *synovial* elements repeat in an atypical fashion the appearance of the normal lining cells of joints, tendon sheaths and bursae when irritated, or in the embryonal state. Thus, they may appear as solid bands or masses of elongated swollen spindle-shaped cells (Fig 4), or with slits or spaces among them. If spaces form, the cells lining them may remain relatively unchanged or they may assume a cuboidal (Fig 3) and sometimes a tall columnar shape (Fig 7). If cuboidal they may heap up and form papillary projections (Fig 1). Regardless of their shape and relationship to spaces, the cells often contain droplets of a material staining red with mucicarmine, which we may assume is hyaluronic acid, since this is the mucin-like material formed by synovial cells.

The *fibrosarcomatous* elements surround and enclose the synovial elements wherever they are present. They may be extremely inconspicuous and resemble a mere supportive framework (Fig 5) or in some areas they may dominate the field to the exclusion of the synovial elements (Fig 6). Generally the cells are hyperchromatic spindles accompanied by reticulin fibers and they form bands or cords (Fig 6). Variations from this are the formation of bizarre forms or cuboidal cells when differentiation is poor. On the other hand, there may be areas in which differentiation is so good that adult fibrocytes and collagen fibers predominate. Calcification may occur in such areas or it may sometimes be found where there is no marked fibrosis (Fig 1). When differentiation is good in a fibrosarcomatous area the synovial elements of the same area usually show a rather high grade of differentiation (Fig 1). The diagnosis of these tumors histologically is generally easy if one is careful to take a number of sections from different areas for in some of them the characteristic features are sure to appear. A single biopsy may, however, fail to show both elements. The only neoplasms with which it may be confused if both elements are found are the hemangio-endothelioma and the chorionepithelioma. The diagnostic feature which will surely distinguish the synovial sarcoma from these two is the ability of its synovial cells to secrete a mucicarmineophilic substance. Neither of the other two are capable of doing this. There is one other lesion of joints which has been confused with synovial sarcoma. This is the formation of a tumor mass within the joint made up of vascular inflammatory and fibroblastic tissue associated with a marked new formation of slit-like spaces lined

with synovial cells. Such lesions closely resemble the synovial sarcomas but they differ in one important respect, neither the synovial cells nor the stromal cells show the morphologic changes which permit one to recognize them as neoplastic. At most, they are hyperplastic. Such tumors, of which we have one example from the knee joint of a 17-year-old girl, might be called benign synoviomias if they could be classified as true neoplasms, but it does not seem proper to suggest this if, as is probable, they are purely inflammatory hyperplasias. As previously stated, the giant cell xanthomatous tumors and the hyperplastic tumors have been included in some reported groups of synovial sarcomas. We do not agree with this and believe that only those cases showing the features above described should have the term applied to them.

**Case 1**—(Table I—No 96) History No 23151 J R, a married woman, age 37, came to the Presbyterian Hospital, August 24, 1915, complaining of a tumor in the right popliteal region. Five years previously she had begun to have pain in this region. It was severe enough to keep her awake at night. Four years previously a swelling was noted in the popliteal region, and the pain gradually disappeared. The tumor grew slowly and continuously. Eight months before admission it had become tender, but was otherwise painless. She had had six children, the most recent eight months previously, and she was still lactating on admission to the hospital. There was an oval tumor in the right popliteal region, extending downwards into the calf. It was firm, elastic, and was not tender. It did not move when the calf muscles were contracted. It measured 15 x 10 x 5 cm. The skin over it was normal except for several dilated superficial veins. The lungs were described as clear, but no roentgenologic examination was made preoperatively. At operation (Dr Hugh Auchincloss), August 25, 1915, a long vertical incision was made over the tumor. It seemed to be encapsulated, and rather soft and hemorrhagic. An attempt was first made to dissect it out from the tissues which surrounded it, but the delicate capsule was repeatedly torn, and the attempt was finally abandoned when the dissection had progressed to the point where it was seen that the internal popliteal nerve could not be freed from the lower pole of the tumor. An amputation just above the knee joint was then performed. On the third day postoperative the patient began to have an elevated temperature, ranging between 101° and 103° F, and complained of pain in her anterior chest. Signs of irregular patchy consolidation over both sides of the chest posteriorly developed, and she began to cough. A roentgenogram showed a number of rounded shadows, some of them as large as five centimeters in diameter, scattered throughout both lung fields. They were beyond doubt metastases. The patient's elevated temperature gradually subsided, her chest pain decreased, and her stump seemed to be healing satisfactorily, until the sixteenth day after operation, when she complained of severe pain in her chest. The next morning she suddenly developed severe dyspnea and cyanosis, and died within half an hour. No autopsy was obtained, but it was presumed that she died of a massive pulmonary embolus.

Microscopically, the fibrosarcomatous elements predominate, and vary tremendously from very fibrous calcified areas to very poor differentiation with round cells. Slits are infrequent. Some are lined with flattened cells, others with cuboidal and occasionally with columnar cells. No mucicarmophilic material demonstrated (Fig 1).

**Case 2**—(Table I—No 97) History No 462118 C S, a 27-year-old pipefitter, came to the Presbyterian Hospital, August 21, 1935, complaining of a tumor of the right elbow. Four years previously he was cranking his car when the engine backfired and he felt something slip in his right elbow. It was painful and slightly swollen for a few days but these symptoms soon disappeared. During the next six months the elbow became increasingly stiffened. He went to a New York hospital where he was

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given an anesthetic and the elbow manipulated. The increased freedom of motion did not last long, however, and within a short time his elbow could not be moved more than about ten degrees. Soon after the manipulation the patient noticed a tumor along the lateral border of the elbow. This slowly increased in size. A week before admission to the hospital he jerked his arm and the resulting pain drove him to seek medical advice. Examination showed the right forearm in about  $130^{\circ}$  of flexion. There was motion by measurement between  $128^{\circ}$  and  $92^{\circ}$ . Supination was full but slightly painful. Only about one-third of pronation was possible. Over the origin of the extensors of the

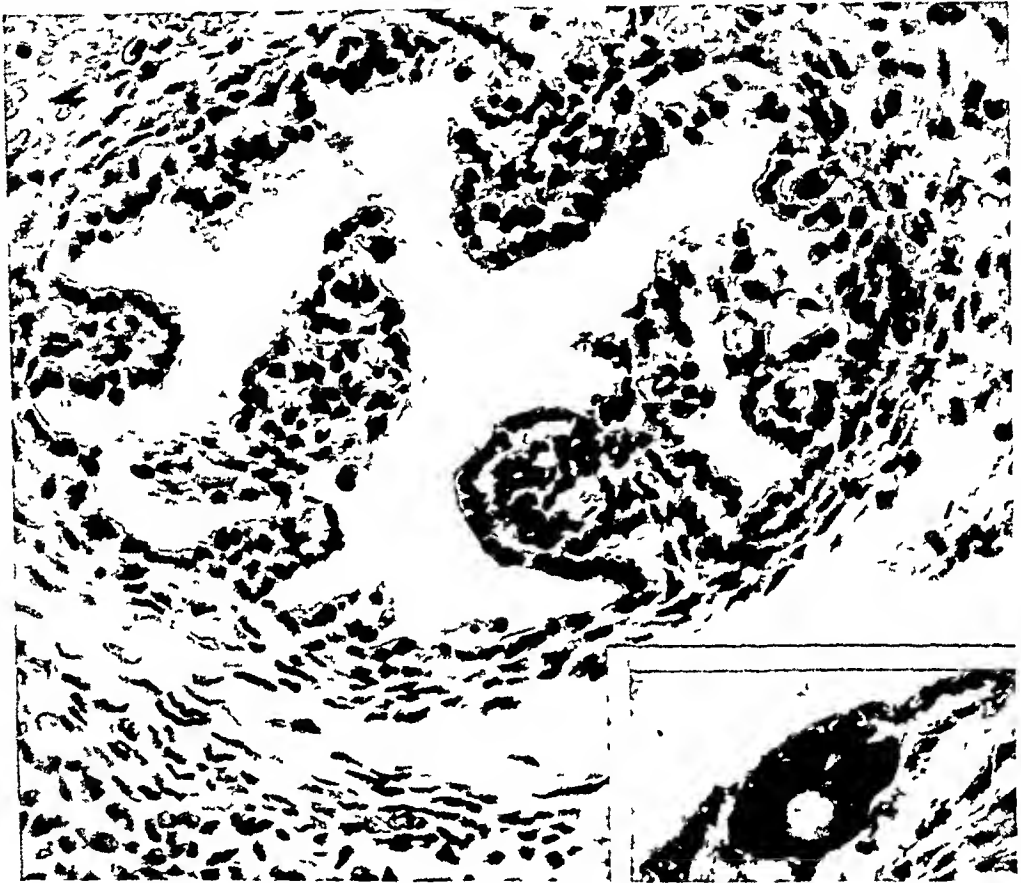


FIG 1—Case 1 (Table I—No 96) Synovial sarcoma of right popliteal region. Photomicrograph ( $\times 410$ ), hematoxylin and eosin stain. A well differentiated synovial tumor structure in which villous processes have been formed. The inset shows an area of calcification in a villous process.

forearm and wrist there was a firm tumor which moved with muscle contraction. Roentgenograms showed a widening of the humeral metaphysis in the supracondylar region, with a bony spur projecting downward and anteriorly from this portion of the humerus. The findings were those of an old united fracture of the humerus. It was assumed that the tumor was a calcified hematoma. Doctor W. Darrach performed an exploratory operation on September 12, 1935. A soft, encapsulated, fusiform tumor mass, measuring  $7 \times 4.5$  cm, was found lying between the brachioradialis and biceps muscles. The radial nerve entered the upper pole of the tumor and its fibers were seen spreading out over its surface (Fig 2). An incision, one centimeter in length, was made into the tumor for biopsy, and several small fragments of friable reddish tissue removed. Frozen sections showed a cellular sarcoma. Further histologic study was deemed desirable before deciding upon the form of treatment, and the wound was, therefore, closed in layers. Study of the 24-hour paraffin sections having shown that the tumor was a synovial sarcoma, amputation through the shoulder was decided upon. This was performed September 14, 1935. Convalescence was uneventful. When he was last seen eight years and eight months later, in May, 1944, he was well and working as

a photostat operator. A roentgenogram of the chest taken at that time did not show any evidence of metastases.

Microscopically, this is a poorly differentiated tumor in which the synovial elements predominate. Slits are many, but small, and lined with undifferentiated cells (Fig. 3). Some contain droplets of mucoid. In the better differentiated areas, the fibrosarcomatous elements become ordinary fibrous tissue and, clothed with synovial tumor cells, form papillary projections into the enlarged spaces.

**Case 3**—(Table I—No. 98) History No. 606261. G. W., a 19-year-old boy, came to the Presbyterian Hospital, April 5, 1940, complaining of a recurrent tumor of the left femoral region. Fifteen months previously, while fencing, he had first noted a small tumor nodule in the left femoral region. On the evening of the same day on which he discovered the tumor, severe pain developed in the groin, and he went to his physician. His temperature was found to be elevated, and he was sent to a local hospital. There, on the following day, the mass in the groin was incised and a large amount of "blood



FIG. 2—Case 2 (Table I—97) Synovial sarcoma of right antecubital fossa. Dissection to show relationship to radial nerve and joint capsule.

and pus" drained. He remained in the hospital 11 days. The wound healed satisfactorily, and after healing was complete no swelling remained. After an interval of ten months, during which he was apparently well, recurrence of the tumor in the femoral region was discovered. It was about the same size as the original tumor, but was painless. After some weeks of indecision, by the doctors he consulted, he was taken to a hospital in another city, where a biopsy was done, and a diagnosis of "fibro-spindle cell sarcoma" was made. The lesion having been considered inoperable, a series of roentgen ray treatments was given. An anterior and a posterior portal were used, each measuring 10 x 15 cm. Treatments were given on January 23, 24, 25, 26, 27, and 29, and on March 19, 20, 21, 22, and 23, 1940. The total dose to the anterior portal was 1944 r, while the posterior portal received 1464 r. The factors used were 200 kilovolts, 50 cm skin target distance, and filter of 2 mm of copper. The radiation failed to produce any change in the size of the tumor, and the patient was brought to the Presbyterian Hospital for consultation. Examination on admission showed an irregularly-shaped, 5 x 8 cm, firm tumor in the left femoral region below Poupert's ligament. The skin over the femoral region was reddened and tanned, and over the center of the tumor there was a vertical biopsy scar. The tumor gave the impression of being an aggregation of small nodules. It could be moved slightly over the deeper structures of the thigh. A roentgenogram of the chest failed to show any metastases. It was

decided to make certain of the nature of the tumor by another biopsy, and this was undertaken on April 12, 1940. When it was exposed, the tumor seemed to be apparently encapsulated, and was soft and reddish. A small piece was excised and the wound closed. The histologic diagnosis was synovial sarcoma. The tumor was situated so high in the thigh that hip-joint amputation would have been inadequate. A hemipelvectomy was discussed, but the surgeon in charge (Dr. Louis Rousselot) decided against it, and in favor of further radiotherapy. Between April 19 and May 15, 1940, he was treated through two portals, a 10 x 20 cm anterior one, and a 10 x 10 cm lateral one. Each received 1900 r. The factors used were 200 kilovolts, 50 cm skin target distance, filter of 2 Mm of copper. There was no discernible change in the size of the tumor following irradiation. The patient refused to return for follow-up after six months and

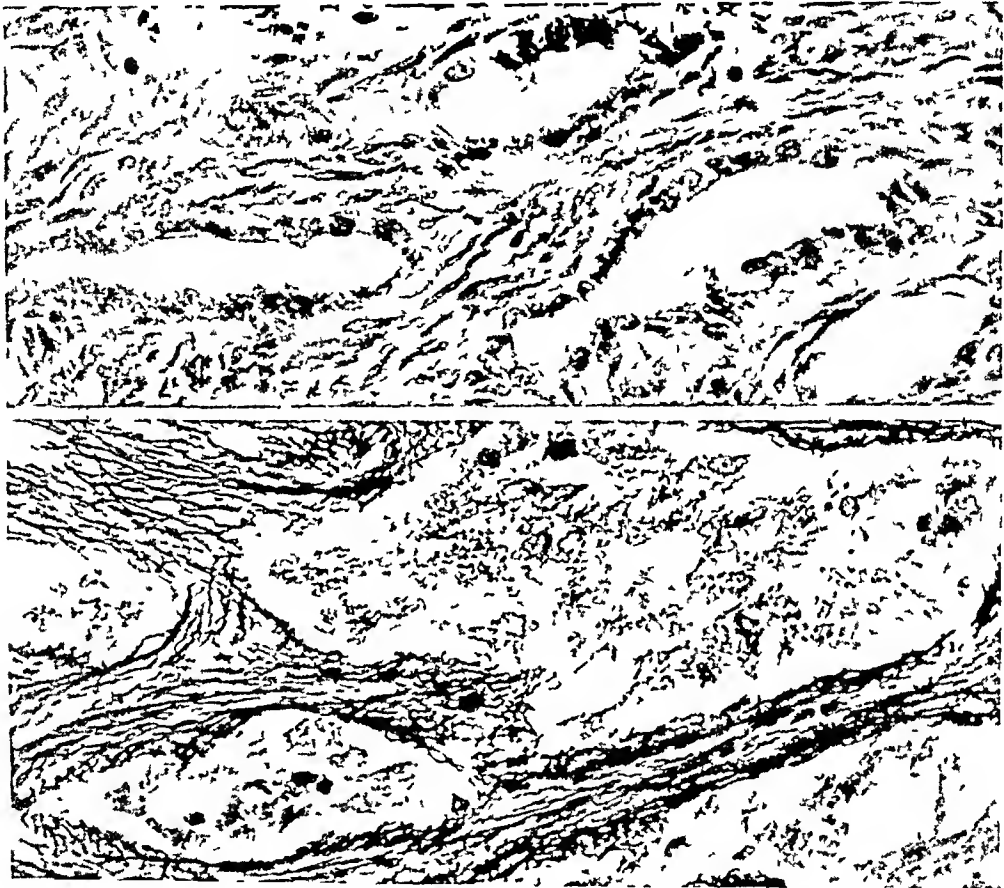


FIG 3—Case 2 (Table I—No 97) Synovial sarcoma of antecubital fossa. Photomicrograph (X 410), hematoxylin and eosin stain above and Laidlaw's silver reticulin stain below. Slits lined by well differentiated synovial tumor cells are scattered through a matrix of spindle shaped cells accompanied by abundant reticulin fibers.

consulted other physicians. He developed lung metastases, and died in April, 1943, five years and five months after the discovery of the tumor. An autopsy was not obtained.

Microscopically, the biopsy shows undifferentiated synovial and fibrosarcomatous areas, with relatively few slits. Mucoid material is present in many of the synovial cells. The synovial cells lining the slits are usually swollen and rounded, but occasionally elongated (Fig 4).

Case 4—(Table I—No 99) History No 493264 W D, a 44-year-old Welsh porter, came to the Presbyterian Hospital, October 27, 1942, complaining of a painful tumor of the left thigh. One year before, while he was helping to lift a truck, the truck slipped and its corner struck him a heavy blow on the left thigh. There was considerable swelling and a large purple area developed in the skin. His physician saw the injury, said there was no fracture, and advised the application of heat



Several days after the injury a tender, doughy mass was noted in the injured area. This tumor persisted without evident change until he came to the hospital. Examination showed a large, firm, but not hard tumor occupying the middle portion of the vastus medialis and the lower portion of the adductor group of muscles of the left thigh. It was moderately tender and immovable. A second similar, but smaller, tumor was noted in the lower part of the rectus femoris. There was slight atrophy of the thigh but no limitation of motion. Roentgenologic studies of the chest and skeleton showed nothing noteworthy. A tentative diagnosis of hematoma of the thigh was made and, October 28, 1942, an exploratory operation was performed by Dr. F. R. Meleney. A vertical incision was made over the lesion, which was found to be a soft, apparently circumscribed, neoplasm. An attempt was made to enucleate it, but was abandoned.

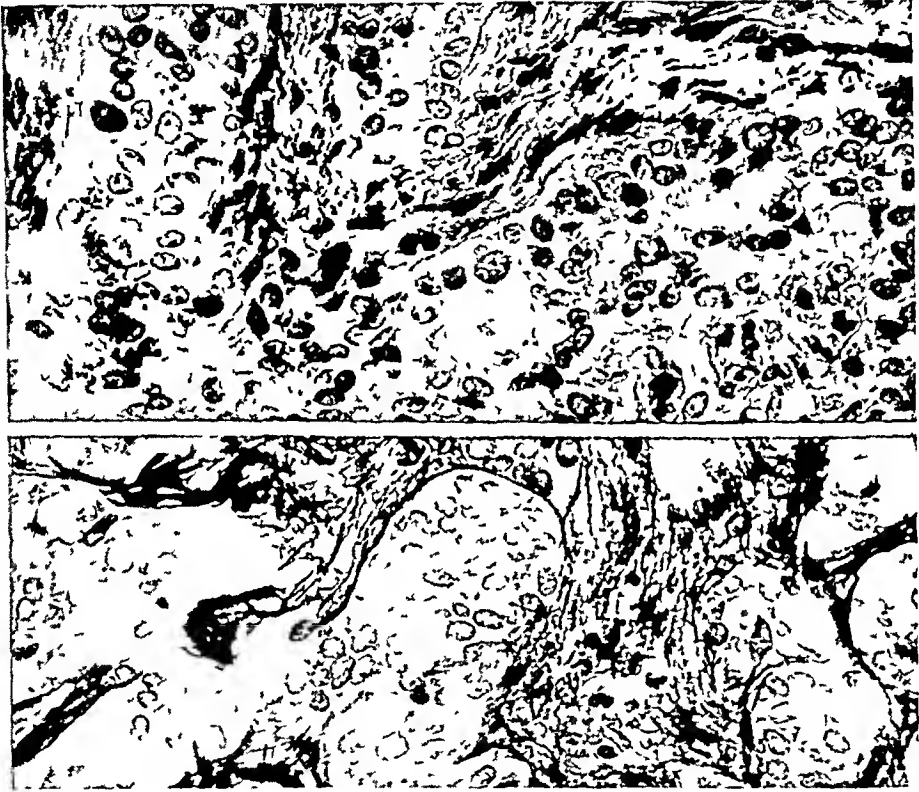


FIG. 4.—Case 3 (Table I—No. 98). Synovial sarcoma of upper anterior femoral region. Photomicrograph ( $\times 410$ ), hematoxylin and eosin stain above and Laidlaw's silver reticulin stain below. The cords of poorly differentiated synovial tumor cells without any fibers among them are separated by slender strands of spindle shaped cells accompanied by numerous delicate reticulin fibers.

when muscle adjacent to the base of the tumor was found to be infiltrated. A biopsy was then removed, which showed, what was thought to be, a fibrosarcoma. Since permission for amputation had not been obtained the operation was terminated. On November 2, 1942, Doctor Meleney performed a hip joint disarticulation. Recovery was uneventful. In February, 1944, the patient was well and working. The tumor measured 8  $\times$  8 cm.

Microscopically, the tumor is largely fibrosarcomatous and there are big areas without any synovial cells but these are plentiful elsewhere. Differentiation is variable in both parts but usually rather poor. Mucoid material is demonstrated in the slits. The synovial cells vary in shape from cuboidal to low columnar (Figs. 5 and 6).

Case 5—(Table I—No. 100). P & S No. 19873 (from Dr. R. Ball). H. R., a male child, age ten, entered a hospital in Chattanooga, Tenn., in 1932, with a 3-cm

## SYNOVIAL SARCOMA

tumor in the left groin. An aspiration biopsy was done, and it was decided to treat the lesion with roentgenotherapy. The tumor, however, continued to enlarge, and during the following four years attained a massive size. There was much calcification within the growth. Local excision was then attempted, but the tumor could be only partially excised. Death occurred in 1938, about six years after the onset of the disease.

Microscopically, the fibrosarcomatous elements predominate in some areas, and in these there is calcification. Elsewhere synovial cells dominate the picture. Spaces are formed occasionally with papillary infoldings and mucoid material. Differentiation is poor and no columnar cells are formed.

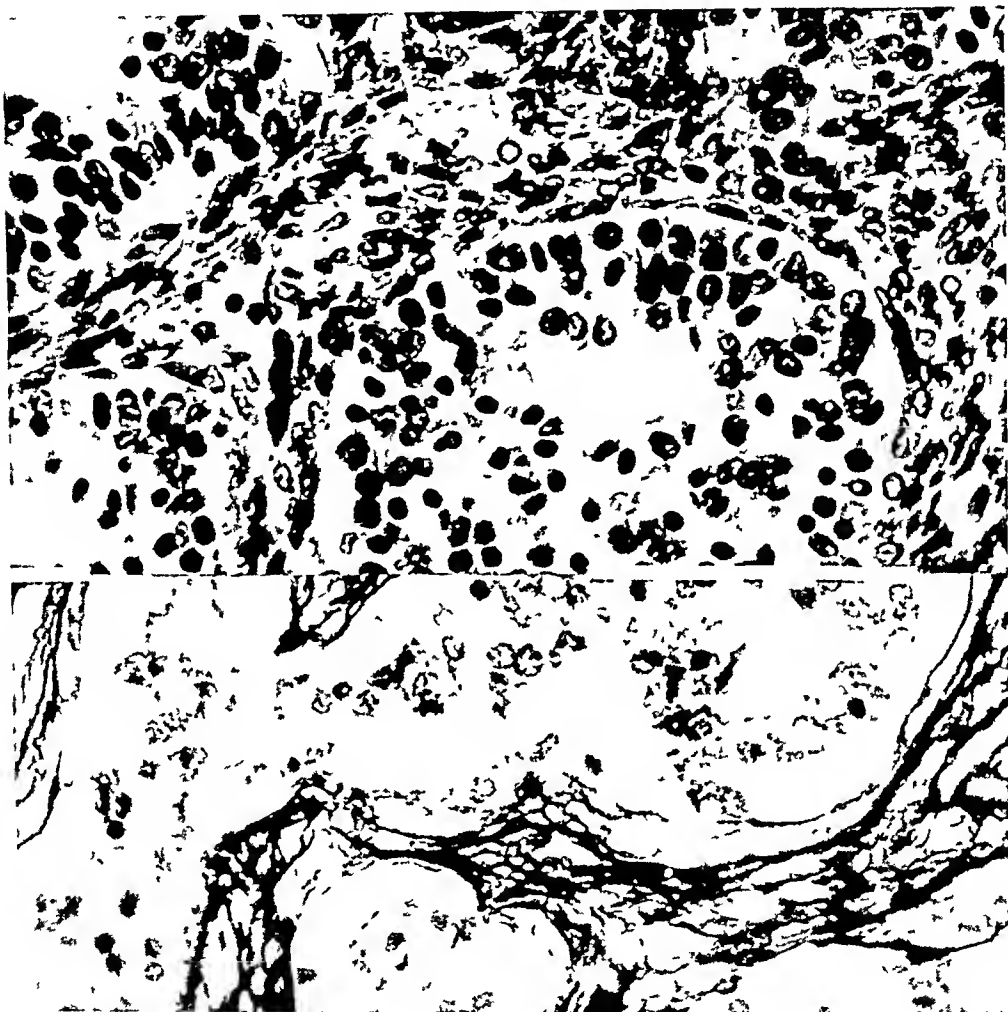


FIG 5—Case 4 (Table I—No 99) Synovial sarcoma of lower medial portion of left thigh. Photomicrograph ( $\times 410$ ), hematoxylin and eosin stain above and Laidlaw's silver reticulin stain below. Portion of the tumor showing characteristic division into synovial tumor cell structures and fibrosarcoma like areas.

**Case 6**—(Table I—No 101) P & S No 17842 (from Dr C Z Garber) M V, —a boy, age five, came to the New York Orthopaedic Dispensary and Hospital in December, 1937, complaining of pain in the left knee. The pain had begun following a blow from a golf club eight months previously. The knee was explored in December, 1937, but nothing more than an hypertrophied fat pad was found. This was excised, but no tumor was found microscopically. Two years later, in January, 1939, three firm nodules, each measuring between 1 and 1.5 cm, were excised from the scar. Pain and tenderness in the knee continued, and it was explored again March 13, 1940, by Dr A DeF Smith. A number of thickened, purplish areas, suggestive of hemangioma, were found in the synovia. The process extended around the cruciate ligaments and into the posterior part of the knee. Frozen section of the tissue removed showed synovial

sarcoma Roentgenograms of the chest were negative Doctor Smith, therefore, performed a midthigh amputation on March 22, 1940 There was no evidence of recurrence or metastases when the patient was last seen in August, 1943, three years and five months after amputation, and six years and four months after the initial symptom of the disease

Microscopically, fibrosarcomatous elements predominate but there are many gland-like spaces lined with tall columnar cells Mucoid is found in some spaces Differentiation is generally good (Fig 7)

Case 7—(Table I—No 102) P & S No 18286 (from Dr R Forsythe) P S, a male, age 28, entered the Grasslands Hospital in September, 1940, complaining of a recurrent tumor of the thigh The original tumor had been present for two or three

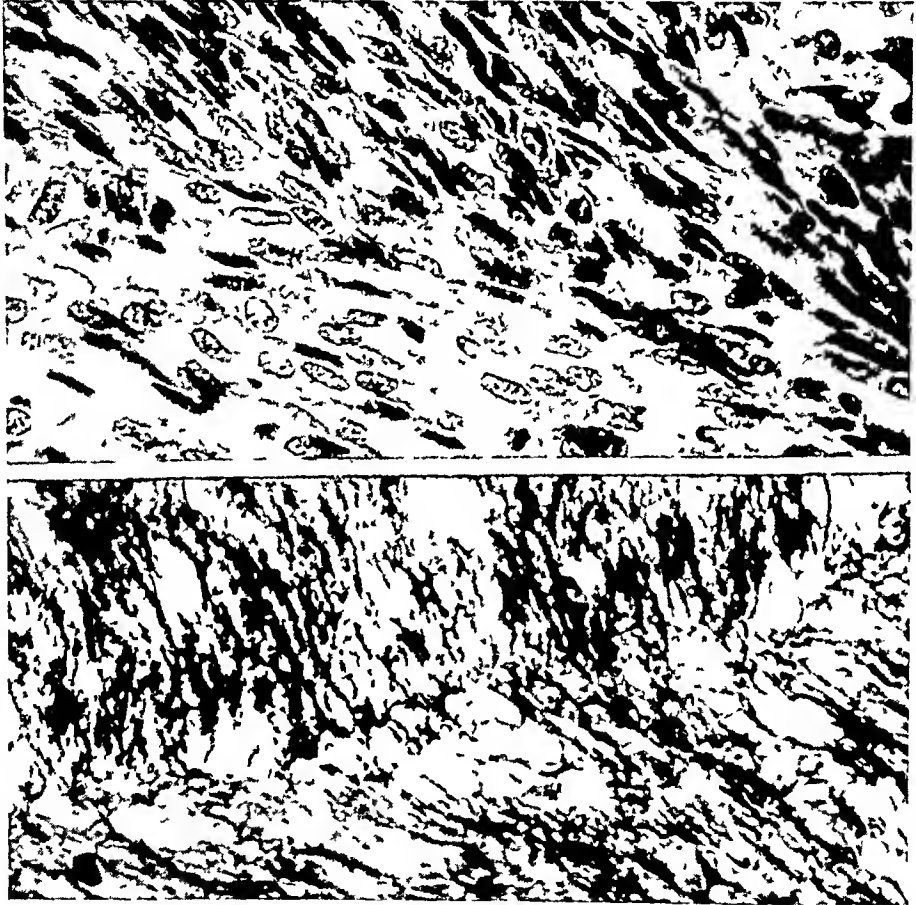


FIG 6—Case 4 (Table I—99) Photomicrograph ( $\times 410$ ), hematoxylin and eosin stain above and Laidlaw's silver reticulin stain below Another portion of the same tumor illustrated in Figure 5 to show a pure fibrosarcoma like area without any differentiated synovial sarcoma cells

months, when it was excised locally in June, 1940, at the Peckskill Hospital The recurrent tumor was in the operative scar, on the medial aspect of the proximal portion of the right thigh Roentgenograms revealed a questionable solitary lung metastasis

Microscopically, the fibrosarcomatous elements predominate, sometimes with the formation of round instead of spindle cells There are very few synovial cells but these form spaces and the cells secrete mucoid material

Case 8—(Table I—No 103) P & S Nos 20119 and 20467 (from Dr Chester Brown) M D, a white female, age 29, came to the Lincoln Hospital in January, 1942, complaining of a tumor on the lateral aspect of the right foot The tumor had been first

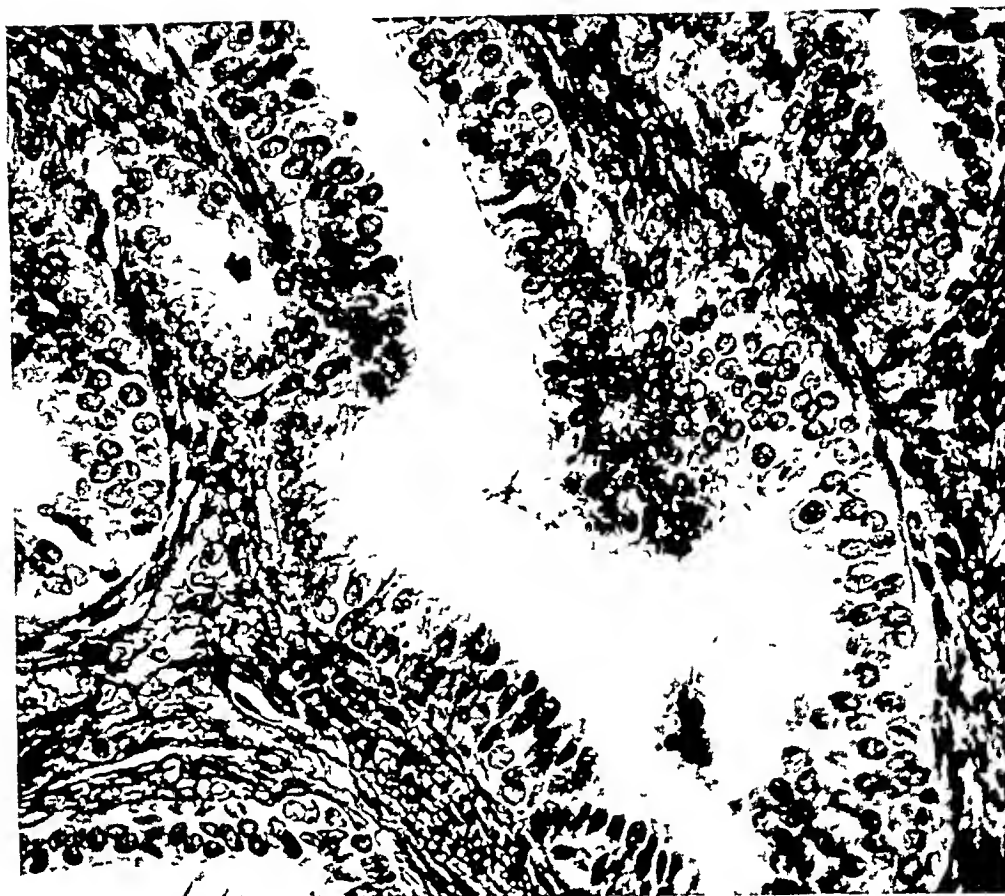


FIG 7—Case 6 (Table I—No 101) Synovial sarcoma of knee joint Photomicrograph ( $\times 410$ ), Laidlaw's silver reticulin stain Synovial tumor cells of columnar shape line the cavities Reticulin fibers abundant but limited strictly to the tissue outside of the synovial cells

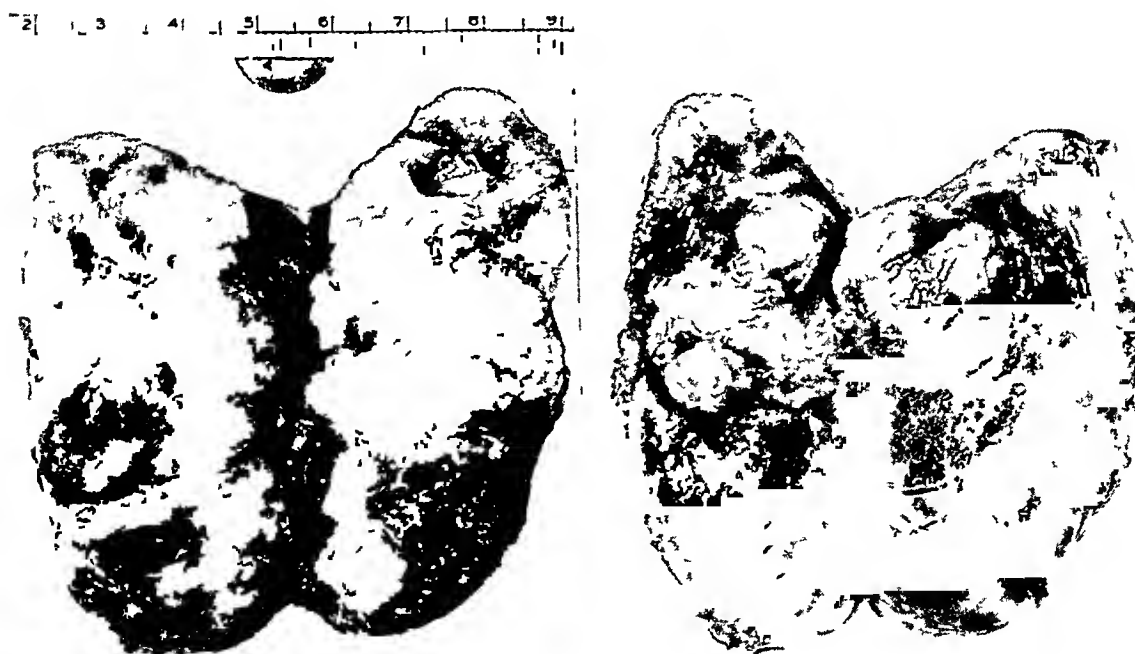


FIG 8—Case 9 (Table I—No 104) Synovial sarcoma of popliteal region (Photograph by courtesy of Dr G H Klinck)

noticed five years previously, in 1927, as a "small pimple" situated on the lateral side of the base of the fifth toe. It gradually enlarged, extending on to both the dorsal and plantar surfaces of the foot. Growth had been more rapid during the three months prior to admission to the hospital, the period corresponding to the duration of her third pregnancy. She had had two previous children, ages four and two, respectively. The tumor had ulcerated a month before her admission. An aspiration biopsy had been attempted at another hospital. Examination showed a large fungating, papillary, bleeding tumor involving the dorsum of the right foot in the region of the fifth metatarsophalangeal joint, growing down between, and spreading apart, the fourth and fifth toes, and extending on to the plantar surface of the foot. The entire tumor measured 10 x 3 cm. Roentgenograms showed pressure erosion of the fifth metatarsal bone. On January 8, 1942, an attempt was made to excise the tumor locally, but it was found that it could not be completely removed. Four months later recurrence was evident.

Microscopically, fibrosarcomatous areas predominate, with formation of some rounded cells, and, differentiation, very variable and peculiar. In only two, out of many, sections do synovial cells appear but these are well differentiated and line cavities containing mucoid material.

Case 9—(Table I—No 104) P & S No 21614 (from Dr G H Klinck and Dr G A Clark) K S, age 31, was admitted to the Samaritan Hospital, Troy, N Y, because of a tumor of the popliteal region. It had been present for eight months and was painless. On February 1, 1943, the tumor was excised locally. It was encapsulated, but it could not be completely removed (Fig 8). The patient refused amputation. Sixteen months later there was a local recurrence, six centimeters in diameter.

Microscopically, synovial cells predominate. There are many spaces, some lined with flattened differentiated cells and others with swollen undifferentiated cells. There is some fibrosis. Very little mucoid material is demonstrated.

*Treatment*—The situation of synovial sarcoma in a limb, and its tendency to remain localized for a long time, are factors that give the surgeon a great advantage in dealing with it. That he has failed to take advantage of this opportunity is clear from the disastrous record of the treatment used in the series of 104 cases which we have reviewed. Only three of the patients were clinically cured more than five years.

The therapy employed has been of four general types: (1) Radiation alone or in combination with surgery, (2) local excision, often repeated several times, (3) excision, or exploratory operation, with an attempt at excision, followed immediately, or within a short time, by amputation, and (4) biopsy followed shortly by amputation. We will discuss these methods of treatment in order.

Radiation appears to have been singularly futile in this disease. It has often been employed, but five-year cure has not been obtained in a single case in which radiation was the chief reliance. In Case 33 in Table I (Coley and Pierson's Case 8), the patient was well six years after treatment, but the radiation treatment was followed by amputation. We have been unable to find any clear evidence that radiation is even of palliative value. In Case 98, in which intensive radiation aiming at palliation was given in our own clinic, there was no definite benefit from it.

Local excision has been the usual treatment. It was undertaken in 84 of the 104 cases that we have tabulated. One of these patients had four local

excisions, six of them had three, and 35 had two attempts at excision. The tumor was usually shelled out by blunt dissection. Sometimes it was removed in fragments. As with other forms of fully malignant sarcoma, any sort of local excision almost always fails to cure. In this series of synovial sarcomas only one of the patients appears to have been clinically cured by local excision. The details of this case (No. 83, reported by Briggs) are as follows. The patient was a woman, age 45, who had a smooth, soft, 6 x 4 x 4 cm, tumor on the lateral surface of the leg about the level of the head of the fibula. It had been present for four years. At operation, it was found to be well encapsulated and was excised. Postoperative radiation was given. She was well seven years later.

Secondary amputation for recurrence following local excision was carried out in 26 of this group of conservatively treated patients. None was cured. Just as in other forms of malignant sarcoma secondary amputation is usually futile, except as a palliative procedure, when local excision has been tried and has failed.

The third type of treatment used in the cases that we have reviewed was excision, or exploratory dissection with an attempt at excision, followed immediately or within a short time by amputation. Here the surgeon relied on primary amputation for cure, but he unfortunately came to this decision only after he had carried out a considerable dissection of the tumor, thereby increasing the likelihood of metastasis. Cases 5, 27, 33, 56, 86, 96, and 99 were treated in this manner. Only one of these patients appears to have been cured, this was Coley and Pierson's patient (Case 33 in our table, No. 8 in their series), a 12-year-old school girl who had a lemon-sized tumor of one year's duration over the left knee. It was explored and excised, and when the nature of the lesion became apparent from histologic study a course of radiation was administered and the leg was amputated. She was well six years later.

Finally, there was a small group of four cases in which a simple biopsy was done, followed shortly by primary amputation when the malignant nature of the lesion became clear from histologic study (Cases 26, 86, 92, and 97). Although the first three of these patients subsequently developed pulmonary metastases, the fourth, our own patient (Case 97), has been well for eight years. This is the longest survival on record following any form of treatment for synovial sarcoma.

We hope that it is more than a coincidence that the longest cure of synovial sarcoma has been obtained by the most radical surgical attack, for it is our firm belief that this is the rational therapy. In a disease in which the results have been as bad as in this one, the surgeon must take courage and use the most radical therapy available. This is a carefully limited biopsy and a high immediate amputation.

The biopsy must be done because it is impossible to diagnose synovial sarcoma, as well as a variety of other deep soft-part tumors, from the clinical picture alone. Moreover, the biopsy must be an incisional biopsy and not an

aspiration biopsy, for the diagnosis of these tumors rests to a considerable extent upon the histologic architecture of the lesion. Diagnosis based upon cytology alone is uncertain. In carrying out the incisional biopsy the dissection should be as limited as possible. It is our preference to make a two- or three-centimeter incision through the skin directly over the tumor. The incision is carried down through the subcutaneous tissue and fascial planes until the periphery of the neoplasm is reached. A small wedge of the tumor, measuring two or three millimeters in width and about one centimeter in length and depth, is then excised with a sharp knife. After careful hemostasis the capsule of the tumor and the fascial planes and skin are closed in layers with interrupted silk. We do not ordinarily rely upon frozen-section diagnosis in these cases, although we often make frozen-sections and study them, for we feel that the differential diagnosis of these soft-part sarcomas is so difficult that permanent sections are necessary in most instances.

It should be emphasized that more extensive exploratory dissection of the tumor, or excision of a larger part of or the whole tumor for biopsy, is undesirable. It may gratify the operator's curiosity about the attachments and extent of the neoplasm but it is a serious threat to the patient's life, for it is possible that metastases may be produced by surgical dissection. A very small biopsy is usually adequate for diagnostic purposes.

The diagnosis having been proved histologically, amputation should be performed promptly. It is important that it be done at a high enough level to avoid local persistence of the disease. Like certain other types of soft-part sarcomas those developing from synovia have a tendency to extend longitudinally between fascial planes a surprising distance in the affected limb. In order to be certain of getting proximal to them amputation should be done at a high level. This means, for synovial sarcoma of the knee for instance, amputation through the upper third of the thigh, and for a lesion of the elbow, amputation through the upper third of the arm.

A final question in the treatment of synovial sarcoma concerns the regional lymph nodes. We have seen no reports of dissection of the regional nodes. Yet there have been seven instances of metastases to inguinal nodes and four cases in which the axillary nodes were involved among those which we have tabulated. Possibly, more complete follow-up data would reveal an even higher incidence of lymph node metastasis. In this respect, synovial sarcoma differs from fibrosarcoma, for the latter metastasizes to lymph nodes so rarely that the phenomenon has no significance in planning treatment. Since regional lymph node dissection is not a hazardous operation it should be seriously considered as a separate and final stage in the treatment of synovial sarcoma.

#### SUMMARY AND CONCLUSIONS

The synovial sarcoma is a rare, highly specialized form of malignant neoplasm which develops in the extremities. It is always composed of two sharply



contrasted tissue forms, one reproducing caricatures of synovial structures, the other resembling fibrosarcoma, and the two are inextricably intermingled. The tumor generally develops slowly, is more commonly found in young adult males, and finally metastasizes usually through the blood stream and occasionally to the regional lymph nodes. Nine new examples are summarized and are analyzed together with 95 previously reported cases. Of this group of 104, only three are known to be free from evidence of persistence or metastasis more than five years after treatment. This study leads to the conclusion that diagnosis should be established by histologic examination of a small fragment obtained by incisional biopsy which causes the least possible trauma. Treatment should be radical—high amputation and possibly regional node dissection. Radiotherapy has been little used and there is no proof that it is effective.

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# SYNOVIAL SARCOMA AND NORMAL SYNOVIAL TISSUE CULTIVATED *IN VITRO*

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AS AN ADJUNCT to clinical and pathologic studies on synovial sarcoma conducted in this laboratory, an attempt has been made to evaluate the cultural characteristics of this neoplasm *in vitro*, and to compare it with normal synovial tissue cultivated under similar conditions

## SYNOVIAL SARCOMA

*Method*—Tissue from three of the tumors described by Haagensen and Stout (Cases 3, 4 and 6) was explanted in lying-drops on cover slips according to the Maximow method. The medium used for cultivation consisted of chicken plasma (sometimes diluted with human plasma) human placental serum, extract of 9–11-day chicken embryos or of adult rat spleen in buffered saline, and serum ultrafiltrate (Simms and Sanders, 1942)

The cultures were washed in the buffered saline three times a week, at which time the liquid components of the medium were renewed. The explants were maintained in their original situation on the flying coverslip as long as possible, in order that the organization and pattern of the outgrowth, as well as its products, might be most advantageously studied. But the fibrinolytic activity of the tumor cells made transferal necessary after one or two weeks. An admixture of human plasma in the clot hastened liquefaction.

Explants from Case 3 were cultivated up to 28 days, from Case 4 up to 36 days, and from Case 6 up to 53 days. During this time they were fixed, at intervals, in 10 per cent formalin, in 2 per cent  $\text{AgNO}_3$  or in Zenker's, Helly's or Bouin's fluid. They were stained with Delafield's hematoxylin, Mallory's phosphotungstic acid hematoxylin, Weigert's hematoxylin with mucicarmine, toluidine blue, fuchsin-ponceau-aniline blue, or impregnated with silver by McKinney's modification of the Bielschowsky method for reticulin.

*Growth Characteristics*—When cultivated *in vitro*, each of these three tumors produced, in varying proportions, two main types of outgrowth—a flat, shelf-like, membranous or epithelioid form, and a tissue composed of rather flattened spindle-shaped cells.

The cells which adopted the membranous habit were broad and flat, often fan-shaped or spidery (Figs 1 and 4) with the ectoplasmic region greatly attenuated. When a culture was impregnated with  $\text{AgNO}_3$ , these cells were shown sometimes to be contiguous, forming a true membrane with a mosaic of black cell borders (Fig 8) and sometimes to exist discretely, only over-

FIG 1

FIG 2



FIG 3

FIG 1—Case 4 Synovial sarcoma 28 days *in vitro* Fixed in Zenker's fluid, stained with Harris hematoxylin Shows spidery type of synovial cell beyond the liquefaction line

FIG 2—Case 4 Synovial sarcoma 12 days *in vitro* Impregnated with silver nitrate to show cell boundaries

FIG 3—Case 4 Synovial sarcoma. 19 days *in vitro* Stained by McKinney's modification of Bielschowsky, demonstrating reticulin formation

lapping here and there (Fig 2) They are rather small compared to epithelial cells, and have large oval nuclei with a variable number of chromatin nucleoli (from two to seven) a scattering which we have found characteristic of mesoblastic cells *in vitro* Division is frequent and is by mitosis The nuclear and nucleolar picture is the same in the spindle-shaped cells of the second type of outgrowth Though they are more often discrete (Fig 9), they may lie parallel and close together forming a sheet, as in Figure 5 The two types of outgrowth, though often distinct, may overlap in the same culture It seems probable that they represent merely two developmental potentialities of the same cell, a cell with capacities rather similar to those of the serosal cell

These tumor cells show a fairly strong fibrinolytic activity, and in a liquefied area of a culture, the edge of the explant is often "healed over" by cells which creep along the surface and extend themselves over it There is a tendency for necrotic patches to develop in the growth and in the explant These appear at the edges as well as in the central portions of the culture, seemingly without reference to the thickness of the area in which they occur We have often observed this in cultures of tumors which are characterized by spontaneous necrosis It seems, also, to occur in the normal joint capsule, though probably as a result of trauma (cf Efskind, 1941), and in the normal serosa as a response to injury (Maximow, 1925) It is not uncommon to find migrant or "metastatic" nodules at varying distances from the explant Sometimes these are seen still connected with the explant by one or two cells pulled thin in the form of a stalk

Reticulin is formed *in vitro* around cells of both types—membranous and spindle-shaped In the former the fibers are exceptionally fine (Fig 3) Conceivably, this fineness may account for the fact that they are not observed between the cuboidal and columnar cells which enter into epithelial formations in the sections of the tumor Reticulin formation in these cultures is rather slow as compared to that by normal fibroblasts

Both early and late in the course of cultivation, and in both types of cells, moderately refractive vacuoles may appear (Fig 9) These become lavender when Nile blue sulfate is applied supravitaly They do not stain with mucicarmine or with toluidine blue Sometimes small cavities lined with cuboidal cells are formed near the border of the explant, containing a fluid similar to the lavender vacuoles

The presence of many wandering cells characterized these cultures These generally fell into the classifications of lymphocytes and macrophages The latter were still present in fair numbers after 24 days *in vitro* They often contained material which stained red with mucicarmine, though the tumor cells present in the same cultures did not

As the culture period advanced, cells which could not be distinguished from fibroblasts appeared, and in some cultures came to form the major part of the outgrowth The origin of these cells is obscure It cannot be said with certainty whether they represent a further modification of the second type of tumor cell, or whether they are the descendants of cells originally

FIG 4

FIG 5

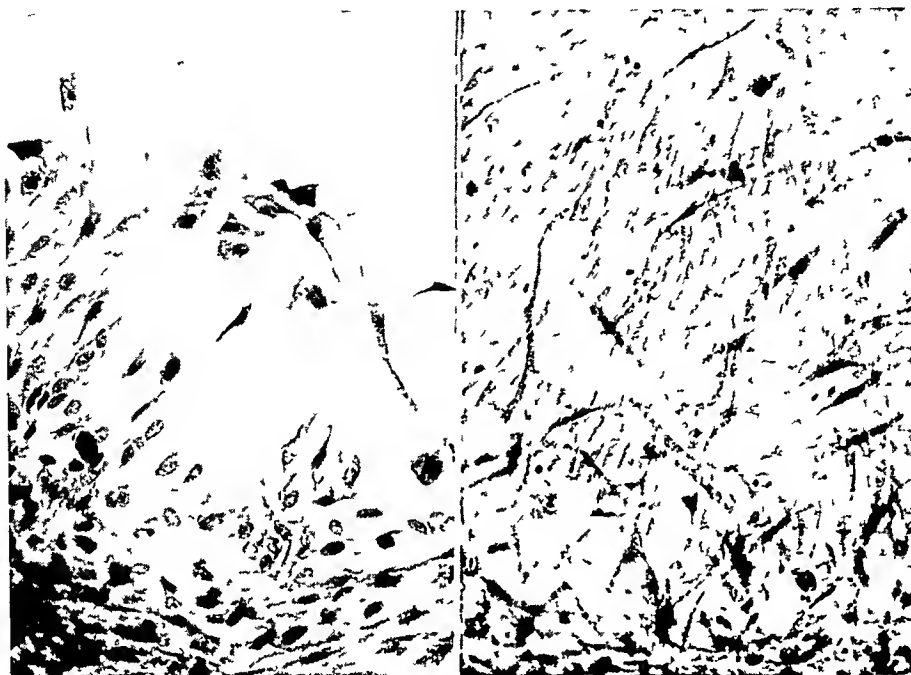


FIG 6

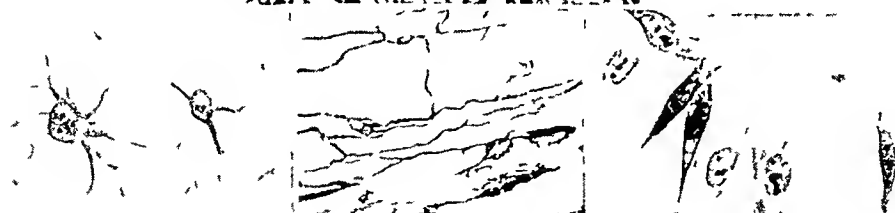
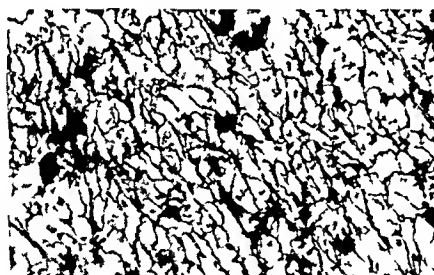


FIG 7

FIG 8

FIG 9

FIG 4—Case 4 Synovial sarcoma 28 days *in vitro* Epithelioid and spidery type of outgrowth Fixed in Zenker's fluid stained with Harris hematoxylin

FIG 5—Case 6 Synovial sarcoma 10 days *in vitro* Flat spindle cell type of outgrowth, note wandering cells Fixed in Bouin's fluid, stained with acid fuchsin ponceau, aniline blue

FIG 6—Synovial cells from knee joint of normal adult rat 15 days *in vitro* Impregnated with silver nitrate to show cell borders

FIG 7—Spidery type of synovial cell from knee joint of normal adult rat 24 days *in vitro* Bouin's fluid, acid fuchsin, ponceau

FIG 8—Case 3 Synovial sarcoma 18 days *in vitro* Impregnated with silver nitrate to show cell boundaries

FIG 9—Case 6 Synovial sarcoma 8 days *in vitro* Spindle cells containing vacuoles which do not stain with mucicarmine Zenker's fixative, Weigert's hematoxylin, mucicarmine

present in the invaded tissue or associated with the blood supply of the tumor. In Case 6, however, where there was a good deal of granulation tissue present in the portion of the tumor obtained for study, the later growth of fibroblasts was greatest. In Case 4, fibroblasts did not appear in the outgrowth except in one slide; the cells were almost entirely of the first, or membrane-forming type. Yet the portion of the tumor adjacent to that from which the explants were made contained almost entirely the interlacing spindle-shaped type of cell, in histologic preparations.

#### NORMAL SYNOVIAL TISSUE FROM KNEE JOINT OF ADULT RAT

The normal tissue was grown by the same method as the tumors. The medium also was the same as used in the neoplastic cultures except for the addition of rat plasma or rat serum.

The growth from the synovial lining of the adult rat knee joint, the patellar and fat pad regions, is of a specific nature. The synovial cell proper appears to be a relatively small one, capable of assuming diverse and transitional forms varying from spindle to spidery to epithelioid. It has a distinct round nucleus which may at times be elongate, depending on the form of cell, with one to four nucleoli (occasionally a cell with five or six is seen). The cytoplasm is somewhat finely granular, although in the early days of culture, large refractive granules can be seen and are rather abundant in cultures where the explant contains fat. As the culture grows older vacuoles may appear within the cytoplasm.

The growth pattern is one of membranes, chains, and wandering cells. The cells of the membrane can be spindle-shaped, spidery or epithelioid, with transitional forms of each (Figs 10, 7 and 11). The spindle-shaped cells may at times be somewhat like fibroblasts. Among the spidery types one may see cells which have a long basal process. The chains, likewise, may be composed of spindle-shaped cells or rounded ones which may have processes. The chains of rounded cells present a bead-like appearance. These chains may branch sidewise, and may broaden by multiplication to produce little islands of tissue along their length (Fig 12). Some of the cells are able to migrate well into the region beyond the general outgrowth. The wandering cells behave rather like macrophages, existing in rounded-up or spread-out forms.

Mitosis is found among the cells of the membranes and chains and probably also may take place among the wandering cells. Amitosis probably occurs. Occasional flattened cells are seen which have two to four nuclei. The cells produce a moderate amount of liquefaction. The fibrinolysis is slow compared to that of epithelial growths.

Lithium carmine, added to the washing saline, showed that some of the cells were capable of phagocytic function, the dye particles being taken up not only by the wandering macrophage-like forms but also as fine granules by epithelioid, spindle and spidery types.

On the basis of this, and, also, because one can see cells which seem to be

FIG 10

FIG 11

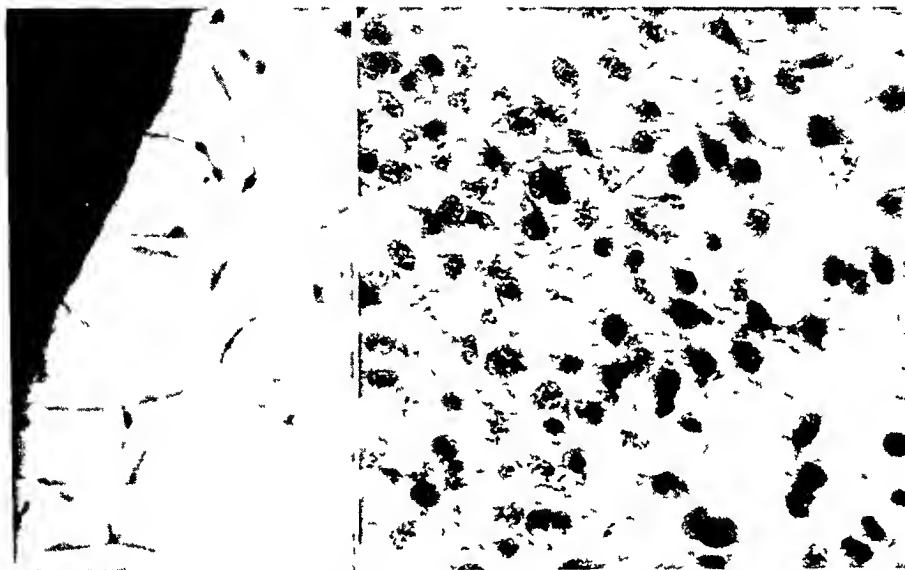


FIG 12

## SYNOVIAL CELL FROM KNEE JOINT OF ADULT RAT

FIG 10—Spindle cells outgrowth at 5 days Helly's fluid, Harris' hematoxylin

FIG 11—Portion of a membranous outgrowth, showing intermediate epithelial and spidery forms 13 days *in vitro* Zenker's fluid, Harris' hematoxylinFIG 12—Growth in chains with island formation "I" Background of epithelioid cells 15 days *in vitro* Zenker's fluid, Harris' hematoxylin

transitional, *i e*, have a typical synovial nucleus and yet appear ameboid, one is led to believe that the synovial cells can assume a macrophage-like form

Supravital staining with neutral red showed granules which were reddened by this dye in all the cell types. In the macrophage-like cells the staining was brilliant. In the other cells the granules were rather fine and usually clumped to one side of the nucleus, but at times were arranged perinuclearly as well. As the age of the culture increased, these granules seemed to become more numerous in the cells. Some of the later appearing vacuoles also were stained by this dye.

Nile blue sulfate also was used supravitaly, and showed bright blue granules of varying size, generally rather large and few in number, scattered throughout the cytoplasm in all the cells.

The cultures were fixed and stained routinely as described for the tumor preparations. Staining with  $\text{AgNO}_3$  revealed borders similar to those found in the tumor cultures (Fig. 6). The McKinney modification of the Bielschowsky method used as in tumor cultures failed to demonstrate reticulin. The use of mucicarmine stain gave negative results.

**DISCUSSION**—Since this paper and the foregoing one (Haagensen and Stout) are concerned primarily with the synovial sarcoma in various of its aspects as a neoplasm, it does not seem suitable to discuss at length here the disputed problem of the nature and relationships of the normal synovial cell. For this the reader may be referred to Petersen's contribution on the joints, in von Mollendorff's *Handbuch der mikroskopischen Anatomie des Menschen*, 1930 (Die Gewebe II, pp. 648–680), and to a more recent summary by L. Efskind (1941).

Judging from the histologic sections of these tumors, we are dealing with a neoplasm in which two morphologically distinct cell types coexist and display cancerous properties. This condition is most nearly paralleled by the mesothelioma, in which, also, two elements, of epithelial and fibrous habit, are the rule (Stout and Murray, 1942).

In the tissue cultures of the synovial sarcomas two cell types and growth habits prevail, though the distinction between these is much less sharp than it appears *in vivo*. From observation of the cultures, one is inclined to conclude that the distinction is not a generic one but that the same cell may potentially assume either form. Bearing on this point is the discrepancy between the sections of the tumor in Case 4, and its outgrowth *in vitro*: the sections showed mainly fibrous tissue, and the cultures almost entirely an epithelioid type of outgrowth. This same situation was encountered in a mesothelioma previously studied (Stout and Murray, 1942), in which the sections were entirely fibrous (resembling a fibrosarcoma) and the outgrowth entirely membranous.

The cultures of normal rat synovium showed the synovial cells to be capable of considerable polymorphism. In general, the human tumor cultures parallel those from the normal rat knee joint as regards form and behavior, though in the latter more diversity of form and more extremely distinctive



cell types are encountered. The characteristic "spidery" form of the synovial cell is frequently reproduced by the tumor cultures. Our normal study confirms the view of Vaubel (1933), that the synovial cell is a specific type of cell, distinct from the fibroblast, and our cultures from the rat's knee reproduce to a considerable degree the forms depicted by him from cultures of synovial cells from the fat-pad of the rabbit's knee. Vaubel regards the synovial cell as most nearly resembling the serosal cell, though being distinct from it. In our study, this appears to be a particularly apt comparison where the tumors arising from these two tissues are concerned.

The fibrosarcomatous component of the synovioma is difficult to reconcile with a view such as Efskind's (1941), derived from the study of stretch preparations of normal and regenerating synovial membranes of the rabbit's knee. He states that the cells of the synovial membrane have no capacity for the formation of fibroblasts, and there are no fibers found among synovial cells. We are inclined to believe that such cells as we see in our cultures exhibiting the typical characteristics of fibroblasts are not synovial cells, but have some other origin. Yet, in the tumor cultures, the membranous type of synovial cell can certainly form reticulin fibers, and the nonepithelial portions of the tumor sections are richly supplied with reticulin. One is reminded of the work of Maximow (1927), and of Schopper (1932), on the serous membranes. Normal mesothelial cells did not form connective tissue *in vitro*, but under conditions of inflammation, and of irritation of the peritoneum by *kieselguhr*, these cells took on the form and characteristics of typical fibroblasts. It may be that in the neoplasm some comparable physiologic state exists.

The continued presence of wandering cells in the tumor cultures after as much as a month *in vitro* is of interest, especially since the normal synovial cells *in vitro* may assume a macrophage-like form. It has been noted that we were not able to produce positive results *in vitro* with the mucicarmine stain except in the wandering cells of the tumor cultures. Nor did we obtain metachromatic staining with toluidine blue. The significance of these negative findings is doubtful, since the technics (especially that of metachromatic staining) are capricious *in vitro* (cf. Davies, 1943).

#### SUMMARY AND CONCLUSIONS

1 Material from three human synovial sarcomas has been cultivated *in vitro*, and its characteristics compared with similarly treated normal synovial tissue from the knee joint of the adult rat.

2 In general, the human tumor cultures parallel those from the normal rat knee joint as regards form and behavior, though the normal cultures exhibit more diversity of form and more distinctive cell types.

3 The normal synovial cell appears to be a specific cell type distinct from other epithelium and from the fibroblast.

4 The synovial sarcoma appears to be a distinct type of neoplasm exhibiting certain similarities to the mesothelioma.

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# PHYSIOLOGIC OBSERVATIONS ON PATIENTS WITH EXTERNAL PANCREATIC FISTULA

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DURING THE PAST TEN YEARS, there have been only rare reports appearing in the medical literature of physiologic observations made upon human subjects with external pancreatic fistula <sup>5, 6, 7, 8, 14, 18, 19, 20, 21, 23</sup> The fundamental information concerning pancreatic function has been derived from the experimental laboratory animal, whereby, with painstaking care, the fundamentals of pancreatic secretion have been investigated <sup>1, 2, 9, 12, 22</sup> Rarely has the clinician been given the opportunity to correlate the physiologic observations made upon the human with the results obtained from the experimental animal The recent advances made in the operative attack upon lesions of the pancreas make it imperative that the surgeon be more conversant with the physiology of that organ, for interference with the normal flow of the external secretion will result in profound alterations in total metabolism

Except for occasional instances, studies made on the human of pancreatic flow and the various constituents of the external secretion have of necessity been done by intubation of the duodenum Therefore, it was a privilege to have at our disposal three individuals each of whom had an external pancreatic fistula

This offered us a rare opportunity to make observations on the influence of such persistent fistulae upon the patients, particularly with reference to the many alterations induced

- 1 General nutritional state of the patient
- 2 Total pancreatic flow in 24 hours
- 3 Pattern of flow in 24-hour period
- 4 Plasma electrolyte pattern
- 5 Plasma protein
- 6 Influence of water intake on pancreatic flow
- 7 Observations on volume flow alterations induced by the administration of various substances into the duodenum
- 8 The effect of intravenous fluids upon pancreatic secretion
- 9 Observations on volume flow alterations induced by the administrations of drugs subcutaneously

These observations, as reported in the statistical study presented in this paper, are concerned with the most productive of these fistulae, but our conclusions are drawn from a survey of the three patients, all of whom reacted similarly

It is well at this time to present the normal values of the individual constituents of pancreatic juice. We consider these normal values, as they were derived from a study of the three individuals previously mentioned who were in widely different states of metabolic balance as far as clinical and laboratory observations were concerned. However, careful analysis of their pancreatic secretions revealed little dissimilarity in composition, and correlated with the isolated reports of the structure of pancreatic secretion appearing in the literature. We feel that these observations and facts are of value, particularly to the surgeon, as they are based upon the study of human secretions, and that emphasis should be put upon their study by the reader, as they have been but rarely called to attention in the past (Table I). Similar studies have been conducted by Krogut, Matzner and Sobel<sup>14</sup>

TABLE I  
ANALYSIS OF PANCREATIC FLUID

Sodium	138 mEq /L
Calcium	2.2-3.2 mEq /L
Chloride	60-80 mEq /L
Bicarbonate	60-75 mEq /L
Total protein	190-340 mg per cent
Albumin	60 mg per cent
Globulin	40 mg per cent
Nonprotein nitrogen	14.3 mg per cent
Urea nitrogen	5 mg per cent
Uric acid	0.2 mg per cent
Nucleoproteins	Not present
Proteose	
Cholesterol	
Sugar	
Sulphates	

The physical characteristics of pancreatic secretion in the human have been previously recorded. It is a clear, opalescent fluid, alkaline in reaction, with a  $p_H$  ranging from 7.5 to 8.0. In addition to the various salts, three chief enzymes are present. These are lipase, amylase and trypsinogen. The secretion of pancreatic juice is known to be under both hormonal and nervous control. The chief effect of secretin is to cause the production of water and inorganic salts. Vagal stimulation results in the secretion of pancreatic juice, but the amount is much less than that produced by secretin. The vagal secretion is thick, scanty, and rich in ferments. The two stimulants are normally effective simultaneously, and the ferments are washed from the alveoli by the tide of alkaline secretin juice.

A brief résumé of the experiences of the three patients is presented to allow the reader an introduction to the type of material used in this study.

**Case 1**—Age 24, developed a pancreatic cyst subsequent to abdominal injury in an automobile accident. Marsupialization of the cyst was accomplished surgically, and a fistula resulted, producing 500 cc of pancreatic secretion in 24 hours.

Flow of pancreatic juice was irregular in quantity and gradually decreased until spontaneous closure occurred about two months after submission to our care.

No significant changes in blood chemistry were found during the latter part of his hospital course except an elevation of plasma chlorides to an approximately normal value of 101.2 mEq per liter.

**Case 2—Age 26** This individual had four episodes of abdominal cramps, nausea and vomiting. A diagnosis of some acute intra-abdominal pathology was made and an incision and drainage of an abscess involving the pancreas and lesser sac was done. Drainage of pancreatic fluid of approximately 100 cc was noted shortly after operation and persisted until admission to our care.

Table III presents an essentially normal pattern. The details of the closure of this fistula are reported elsewhere.

**Case 3—Age 25** This patient sustained a gunshot wound of the upper abdomen, one of the sequelae of which was an external pancreatic fistula. This persisted in spite of attempted surgical repair elsewhere, and at the time of admission to our care was productive of large quantities of pancreatic fluid.

Table IV is a presentation of the marked changes in blood constituents found in this individual. The apparently normal values of some of these constituents will be shown to be misrepresentations, as will be explained subsequently.

TABLE II

## BLOOD STUDY OF CASE 1 AT THE TIME OF RECEPTION IN HOSPITAL

R B C	5,080 000 per cu mm
W B C	12 300 per cu mm
Hb	90 0 per cent
Hematocrit	46 8 per cent
Sed rate	0 60 mm /min
N P N	24 8 mg per cent
Serum protein	6 97 gm per cent
Serum albumin	4 50 gm per cent
Serum globulin	2 47 gm per cent
Chloride	96 0 mEq /L
Carbon dioxide combining power	30 9 mEq /L
Prothrombin time	26 0 secs

TABLE III

## BLOOD STUDY OF CASE 2 AT THE TIME OF RECEPTION IN HOSPITAL

R B C	4 280 000 per cu mm
W B C	6 200 per cu mm
Hb	12 4 gm per cent
Hematocrit	38 8 per cent
Sed rate	0 6 mm /min
N P N	28 9 mg per cent
Serum protein	6 85 gm per cent
Sodium	140 6 mEq /L
Chloride	103 0 mEq /L
Carbon dioxide combining power	31 2 mEq /L

TABLE IV

## BLOOD STUDY OF CASE 3 AT THE TIME OF RECEPTION IN HOSPITAL

R B C	5,080 000 per cu mm
W B C	12,200 per cu mm
Hematocrit	44 per cent
Sed rate	1 88 mm /min
N P N	40 0 mg per cent
Serum protein	7 96 gm per cent
Serum albumin	4 92 gm per cent
Serum globulin	3 04 gm per cent
Sodium	113 3 mEq /L
Chloride	91 2 mEq /L
Carbon dioxide combining power	16 3 mEq /L

GENERAL NUTRITIONAL STATE OF THE PATIENT

The general nutritional state of these individuals is directly proportional to the severity of the fistula. The first patient had experienced rather marked weight loss which at the time he came under our care he had partially regained. Gradual diminution in flow of the fistula was accompanied by increased appetite and gradual increase in weight. By the time closure of the fistula occurred, normal weight had been restored.

This parallelism in weight and pancreatic secretion loss is demonstrated in the fact that the second of these individuals, who was losing the least amount of secretion, presented the least alteration of body substance.

The loss of large amounts of pancreatic secretion in the third individual produced a profound alteration in physical appearance, with marked reduction in weight, and was associated with a symptom complex not unlike that demonstrated in Addison's disease.

Inasmuch, as the metabolic and physiologic changes evidenced in the first two patients were minimal, we will confine ourselves to reports concerning the reactions of Case 3.

TOTAL PANCREATIC FLOW IN 24 HOURS

The total quantity of pancreatic juice excreted in 24 hours was the first problem to attract our attention. Estimates of other investigators have placed the daily amount of pancreatic flow into the duodenum in a range varying from 500 to 1500 cc, with the usual figure for man being accepted as 700 cc. In 27 investigations of external pancreatic fistula reviewed by McCaughan, Sinner and Sullivan,<sup>20</sup> the least amount of pancreatic juice secreted from an external fistula was 30-40 cc per day and the largest 1384 cc. Our individual produced through an external fistula amounts ranging as great as 1770 cc per day. It should be stated that intestinal digestion in this patient was not disturbed, and that stools were normal in appearance and fat content. Therefore, the fistula was not total in nature, and the justifiable assumption was made that enough pancreatic secretion to provide for intestinal needs was being delivered into the duodenum. This might bring the total quantity of daily secretion to 2400 cc a day, or perhaps more, if the usual accepted quantity of 700 cc necessary for digestion is added to the amount lost externally by this individual. This last figure, which is about four times the value previously accepted as normal for total volume secretion in 24 hours, is great enough that the physiologic aspects of pancreatic secretory volume must be reevaluated.

PATTERN OF FLOW OF PANCREATIC SECRETION IN 24-HOUR PERIOD

Chart 1 does not represent the consolidated pattern of flow of pancreatic secretion for all of the days the patient was under observation but is a representative day in which the patient was on a high caloric diet, ingesting supplemental liquids as his appetite dictated without supervision or suggestion on the part of the hospital staff.

It will be observed from studying Chart 1 that the volume flow during the daytime was greater than night, and postprandial secretion showed a decided increase

Fever has been reported as being a cause of diminution of flow. It was our observation that fever in itself was not the cause of diminution of flow but a symptomatic manifestation of obstruction of the fistula. This phenomenon was repeatedly seen

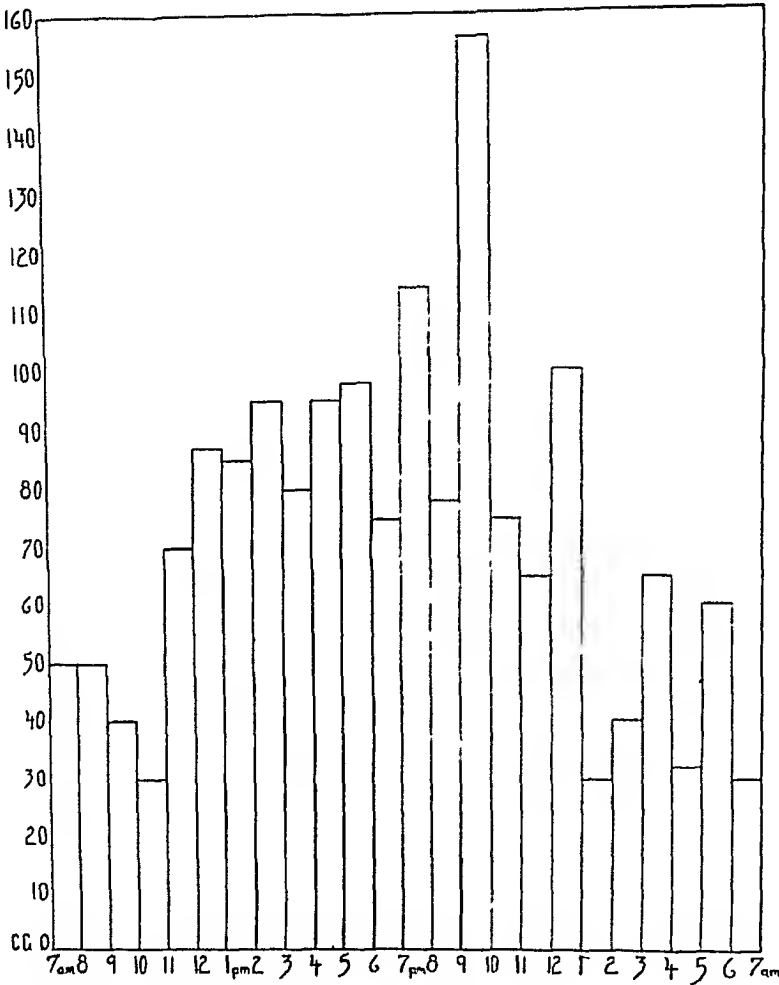


CHART 1—Case 3 Pattern of flow of pancreatic secretion in 24 hours

#### PLASMA ELECTROLYTE PATTERN

The results of severe continued loss of pancreatic fluid containing large amounts of electrolytes produce changes in plasma electrolyte pattern, as presented in Chart 2

#### *Sodium*

The marked loss of sodium ion from the body through the external pancreatic fistula had lowered the concentration of this ion in the blood plasma from a normal of 142 mEq/L to 113.3 mEq/L

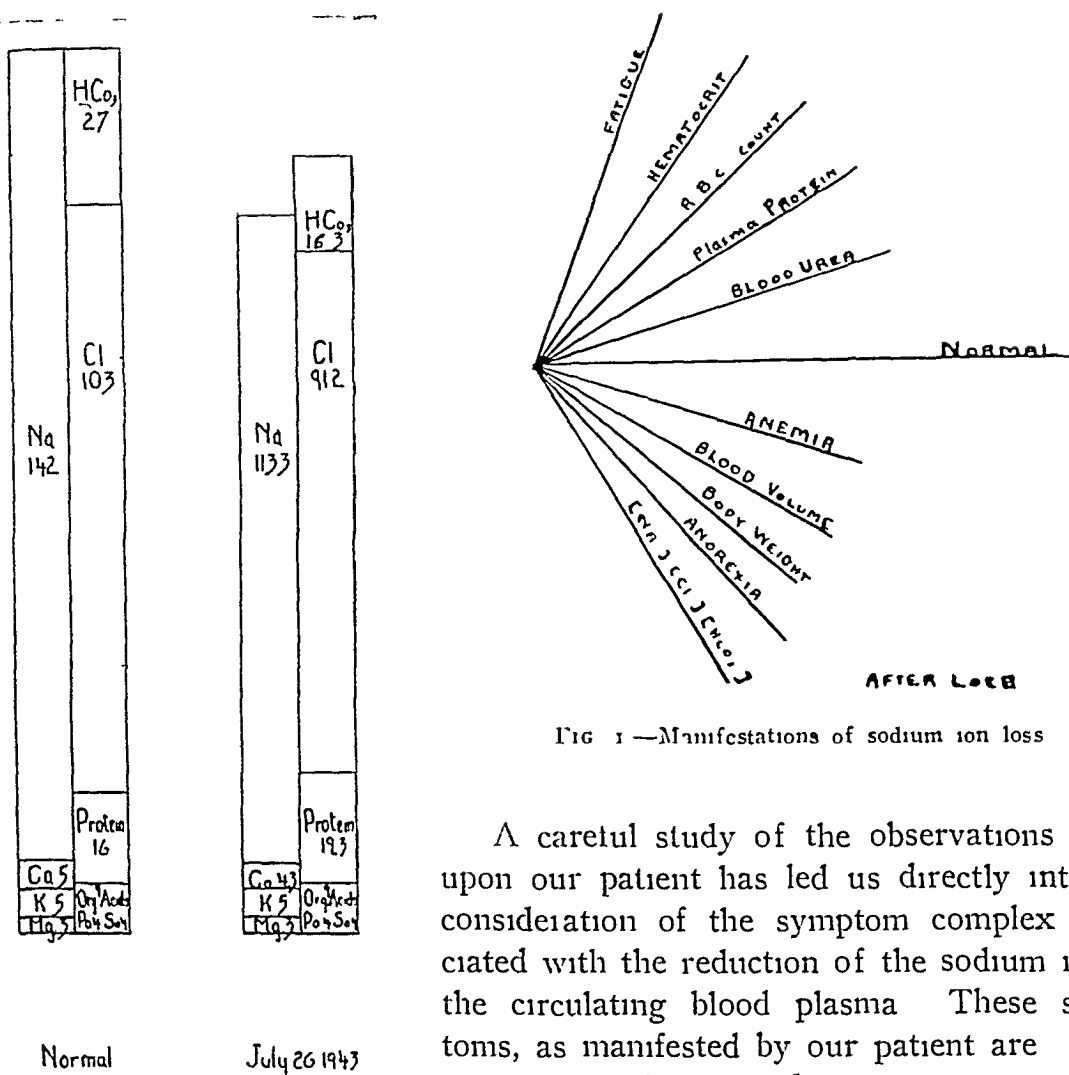


FIG 1 —Manifestations of sodium ion loss

A careful study of the observations made upon our patient has led us directly into the consideration of the symptom complex associated with the reduction of the sodium ion in the circulating blood plasma. These symptoms, as manifested by our patient are Lethargy, mental torpidity, anorexia, nausea, fatigue upon slight exertion, and marked dehydration.

A study of the allied blood findings associated with sodium deficiency in the circulating blood plasma in this individual reveals great

similarity to the state manifest in experimental sodium chloride deprivation in the human, Addison's disease, and in the adrenalectomized animal.

McCance<sup>16</sup> produced sodium deficiency in experiments upon the human and found that the following changes in the blood occurred. There was a rise in erythrocyte count, hemoglobin, red blood cell volume and plasma protein concentration. These alterations occurred coincidental with a marked decrease in the sodium ion concentration in the blood plasma. These were interpreted to represent the manifestations of a loss of extracellular fluid. The symptomatic manifestations of this deprivation were expressed in a drop in circulating fluid, the sense of loss of taste, anorexia, nausea, fatigue and a marked sense of exhaustion, with dulling of the mental faculties.

Addison's disease is associated with a marked reduction of sodium ion in the circulating medium. This loss of sodium, and secondary loss of water, occurs through the kidneys and may be sufficient to produce profound



alterations in extracellular fluid distribution, as evidenced by low blood volume, high hemoglobin concentration and elevated serum protein values

The importance of sodium loss in adrenalectomized animals was first pointed out by Loeb, and his associates<sup>15</sup> Many of the characteristic changes in certain aspects of metabolism, circulation and blood concentration, found by these investigators, were also noted in the individual under study

It is our feeling that the effects of the loss of sodium are fundamentally the same whether it be experimentally through the skin, through the kidneys, as the result of removal of the adrenals, or as in our patient, by loss through an external pancreatic fistula

The fact that these effects were due to a loss of sodium in our individual was proven by a reversal of the changes enumerated above when the sodium deficiency was completely corrected

### *Calcium*

We believe that we have encountered a phase of calcium metabolism which has not received the attention it deserves It is generally recognized that calcium is absorbed in the upper intestinal tract and that it is excreted in the urine<sup>17</sup> and the feces<sup>11</sup> It is the opinion of some observers that fecal calcium is calcium which has never been absorbed from the intestinal tract However, it is the feeling among others that calcium is absorbed in the upper intestinal tract and later excreted through the large bowel<sup>3</sup> Animals on a calcium-free diet will excrete calcium into the intestinal tract<sup>3</sup> This calcium comes from the extracellular fluid and has previously been liberated from bone, as indicated by osteoporosis

We have, as have other investigators,<sup>14</sup> found that calcium is excreted in pancreatic juice draining from an external fistula At one time 2.2 mg per cent and another 3.24 mg per cent were found in the pancreatic secretion Ordinarily this would be discharged into the duodenum This fact would indicate that a cycle of calcium conservation is present in which the ionizable calcium in the extracellular fluid is discharged into the upper intestinal tract in the pancreatic secretion This, as previously indicated, is in the secretin fraction of pancreatic secretion A fraction of the calcium discharged into the upper intestinal tract in the pancreatic secretion may be absorbed, the remainder may pass out in the feces

This calcium exists as ionizable calcium as distinguished from calcium which is nonionizable or protein-bound The former is free to diffuse from the blood plasma into the other extracellular fluids The calcium content of the latter is of necessity lower than that in blood plasma as protein-bound calcium cannot pass across the cell membrane

The total blood calcium of this individual on one occasion was 8.6 mg per cent, and the calcium determination made on a pooled specimen of pancreatic fluid was 3.24 mg per cent It is generally recognized that 55 per cent of calcium in plasma is in diffusible form<sup>3</sup> Evaluation of the figures obtained of the observations in this individual reveals that a process of filtration may

be occurring, inasmuch as the value of 3.24 mg per cent diffusible calcium found in the pancreatic secretion approaches the calculated value of 4.73 mg per cent of diffusible calcium for this individual

### *Chloride and Bicarbonate*

A marked decrease in plasma chloride had occurred, as evidenced in Chart 2, with a fall from 103 mEq/L to 91.2 mEq/L as a result of the continued loss of 60–70 mEq/L in the pancreatic secretion. This loss of chloride did not directly parallel the loss of sodium because of the large amounts of bicarbonate lost in pancreatic secretion.

Pancreatic secretion has an alkaline  $p_H$  ranging from 7.5 to 8. This is thought to be due to the high concentration of bicarbonate found in the secretion, the figure for bicarbonate being 60–90 mEq/L whereas, in the blood, it exists in a normal concentration of approximately 27 mEq/L. Our patient, however, had a blood concentration of bicarbonate of 16.3 mEq/L.

This is a manifestation of the continued drain on tissue reserves of chloride and bicarbonate which were being continually lost from the body by the disturbed mechanism of chloride and bicarbonate conservation which normally exists through reabsorption of pancreatic secretion from the bowel.

We had expected that the appearance of chloride and bicarbonate in the pancreatic secretion would be in approximately the same ratio in which they appeared in the blood plasma. The fact that this parallelism did not exist was surprising to us. We observed that the sum of the mEq/L of chloride and bicarbonate closely approximated that of sodium, with preservation of ionic balance across the membrane. This fact is a manifestation of the preservation and economy of chloride ion retention in the blood plasma. It has been seen that the concentration of bicarbonate in the pancreatic secretion is approximately four to five times that in which it exists in the blood plasma. An explanation of this unexpectedly high value for bicarbonate concentration in the pancreatic secretion has been presented by Komarov, Langstroth and McRae,<sup>13</sup> who state that the increase in bicarbonate ion concentration in pancreatic juice observed with increasing activity of the gland is due to the increased rate at which carbon dioxide is formed as a metabolic product within the gland. On this basis, a part of the bicarbonate ion has its immediate origin within the secretory cells. These observers, likewise, noted that the increase in bicarbonate ion was accompanied by a decrease in chloride ion concentration to such an extent that the sum of both in mEq/L remained relatively constant.

The following is suggested as an explanation of this phenomenon by the above mentioned authors:<sup>13</sup> "A difference in net ionic charge on two sides of a membrane results in an electrical potential difference across it. This potential difference facilitates the passage into the cell of ions of one sign, but hinders that of ions of the other. An increased rate of formation of anions ( $\text{HCO}_3^-$ ) within a cell, due to increased metabolism, results in a change in the potential difference favoring more rapid passage of cations ( $\text{Na-K-Ca}$ )

but retarding the passage of anions ( $\text{Cl}$  and  $\text{HCO}_3$ ) from the blood stream or tissue fluids. Since the cations already pass easily through the membrane at the maximum rate (the concentrations in the secretion are comparable with those in the serum), the principal effect is a retarding of the passage of anions, and so appears a decrease in the  $\text{Cl}$  concentration of the secretion."

Further support to this theory is given by the observation in our series that where glandular activity increased carbon dioxide combining power of the secretion increased and chloride concentration diminished (Table V). We also observed the converse of this phenomenon (Table VI).

TABLE V  
DETERMINATIONS ON PANCREATIC SECRETION FOLLOWING INTRAVENOUS ADMINISTRATION  
OF 5 PER CENT GLUCOSE IN PHYSIOLOGIC SALINE\*

	Carbon Dioxide Combining Power	Chloride	pH
Control	54.6	78	7.5
After 1000 cc	80.8	51	8.0
After 2000 cc	80.8	51	8.0

\* The above figures are mEq./L. for pancreatic secretion

TABLE VI  
DETERMINATIONS ON PANCREATIC SECRETION FOLLOWING HYPODERMIC ADMINISTRATION  
OF VARIOUS DRUGS\*

	Carbon Dioxide Combining Power	Chloride
Control	54.6	78
Ephedrine	57.3	67
Pilocarpine	34.9	67
Atropine	27.2	51

\* All the above values are expressed in mEq./L. for pancreatic secretion showing alteration in electrolyte composition following subcutaneous injection of the indicated drugs

#### PLASMA PROTEIN

The maintenance of a normal body fluid volume is dependent upon the presence of adequate amounts of fluid, electrolytes and protein. Alteration in any or all of these constituents produces profound changes.

Pancreatic fluid containing water, electrolyte and protein, was lost through the external fistula. In addition, the proteins necessary to retain fluid in the circulating blood volume were depleted from lack of protein ingestion and by the presence of infection.

With the shrinkage of effective blood volume, there is a false relative rise in the concentration of plasma protein, though the actual total amount of circulating protein is much below the calculated normal for that individual. This phenomenon has been commented upon previously by Gamble.

The initial studies of protein, hematocrit, and erythrocyte count in this individual were 7.96 Gm. per cent, 44 per cent, and 5,080,000 per cu. mm., respectively. How normal these figures appear, except for a slight elevation in protein concentration. Mere observation of the individual told one that these carefully made laboratory determinations did not present an accurate picture of the metabolic state. He was emaciated and dehydrated, his entire

action impressed one with the fact that here was an individual whose bodily stores were depleted to the breaking point, and who, in paradoxical fashion, presented a normal blood picture for these constituents. He was in vibrant health in the laboratory, but practically dead on the ward.

It is unfortunate that the means for determination of total extracellular fluid and blood volume were not at our disposal. It is in a case such as this that determinations of extracellular fluid and blood volume are of inestimable value. A correct lead would have immediately been presented from their study. Additional information can be obtained from the determination of the concentration of other blood constituents such as sodium, chloride, and bicarbonate. We feel that information concerning the concentration of the latter three constituents offer a more accurate picture of the true physiologic state in the dehydrated individual than the more usually employed procedures of protein determination, hematocrit, and erythrocyte count. Where total fluid determinations can be obtained, they should invariably be made.

With clinical improvement of the individual, it was noted that the concentration of protein, the hematocrit, and the erythrocyte count became lower. This was an expression of the fact that the circulating blood volume was gradually increasing and dilution of these elements was present. It was only when the individual was able to move into a positive phase of protein and erythrocyte production and when the blood volume had approached normal, that a true rise in concentration of these constituents was found. This phenomenon is mirrored by the fact that the concentration of the various electrolytes—sodium, chloride, and bicarbonate—rose in parallel fashion to normal level.

In the preceding paragraphs, we have recorded the physical appearance of this individual upon reception at the hospital, and explained the factors concerned in the production of the clinical syndrome manifesting itself as "Addison's disease" without adrenal pathology associated with the marked sodium ion loss present in the most productive external pancreatic fistula recorded. We have, in addition to this, outlined the factors involved in the alteration of the general electrolyte pattern and plasma protein values of this patient. Failure to correct these marked changes in fluid balance, electrolyte concentration and plasma protein values would have been lethal. Restitution of sodium ion associated with the administration of substances to maintain the ion in the circulating fluid volume, which must also be made adequate, will bring the individual to a metabolic normal. Physiologic saline, citrated whole blood and blood plasma, combined with a diet complete in various details will restore such an individual to a metabolic balance. Adequate amounts of the various vitamins, iron and calcium are indicated. The administration of a solution of sodium bicarbonate is unnecessary as bicarbonate ion is provided in satisfactory quantity as a by-product of the respiratory processes. As a matter of record, this unusually large fistula closed spontaneously upon restoration of the individual to a normal metabolic state, with particular reference to water balance, electrolyte pattern and plasma

protein concentration Restoration of all three factors must be coordinated as it is impossible to individually correct one and achieve success

#### OBSERVATIONS ON VOLUME FLOW ALTERATIONS INDUCED BY THE ADMINISTRATION OF VARIOUS SUBSTANCES INTO THE DUODENUM

During the period in which the patient was being restored to a normal metabolic state, a series of experimental studies were made The first of these series of observations were conducted with a gastric and duodenal tube in place Constant negative water suction was maintained on the gastric tube to prevent discharge of gastric contents into the duodenum

TABLE VII  
DETERMINATION ON PANCREATIC SECRETION\*

	Carbon Dioxide Combining Power	Chlonde
Control	60 76	66 2
225 cc warm water	39 82	67
225 cc chicken broth	58 58	71 5
2 cc 10 per cent HCL in 100 cc water	73 33	60 5
50 cc 10 per cent NaHCO <sub>3</sub>	58 71	62 5
50 cc olive oil	57 3	79 7
50 cc 50 per cent glucose	30 33	57

\* All the above values are expressed in mEq /L for pancreatic secretion showing alterations in crystalloid composition following administration of substances indicated through a duodenal tube

#### *Water*

Two hundred twenty-five cubic centimeters of warm water was introduced into the duodenum through a duodenal tube Regurgitation of water into the stomach did not occur, as fluid could not be aspirated through the gastric tube A fall in the amount of pancreatic fluid from 12 4 cc to 7 1 cc and 7 4 cc in successive 15-minute periods was observed The acid gastric material was prevented from reaching the duodenum or was reaching it in extremely small quantity because of the constant suction supplied through the gastric tube It is assumed that the duodenal contents were less acid due to dilution and that less stimulation to pancreatic secretion *via* the prosecretin mechanism resulted (Chart 3)

#### *Hydrochloric Acid*

It is well recognized that the introduction of acid gastric chyme into the duodenum will stimulate the flow of pancreatic juice through the pancreatic prosecretin-secretin mechanism Therefore, we were not surprised that the deposition of hydrochloric acid directly into the duodenum produced an increase in the amount of pancreatic juice secreted Thirty minims of 10 per cent hydrochloric acid in 100 cc of warm water were introduced directly into the duodenum through a tube The flow of pancreatic juice which had dropped to a low of 0 2 cc in 15 minutes during the course of a series of experiments rose rapidly to 18 6 cc, and subsequently 16 4 cc during the next 15-minute period This series of events substantiated the fact that pancreatic flow is stimulated by the presence of acid in the duodenum in the human as it is in animals These observations confirm those made by McCaughan,, Sinner and Sullivan,<sup>20</sup> in 1938 (Chart 3)

*Sodium Bicarbonate*

The counterpart of the administration of hydrochloric acid into the duodenum was undertaken by introducing 50 cc of a 10 per cent solution of sodium bicarbonate through the duodenal tube. An immediate fall in secretion from 10.6 cc to 6.1 cc and 2.4 cc was noted in successive 15-minute periods. The rise in  $p_H$  of the duodenal content reflected lessening of acid stimulus to secretion, caused drop in output (Chart 3)

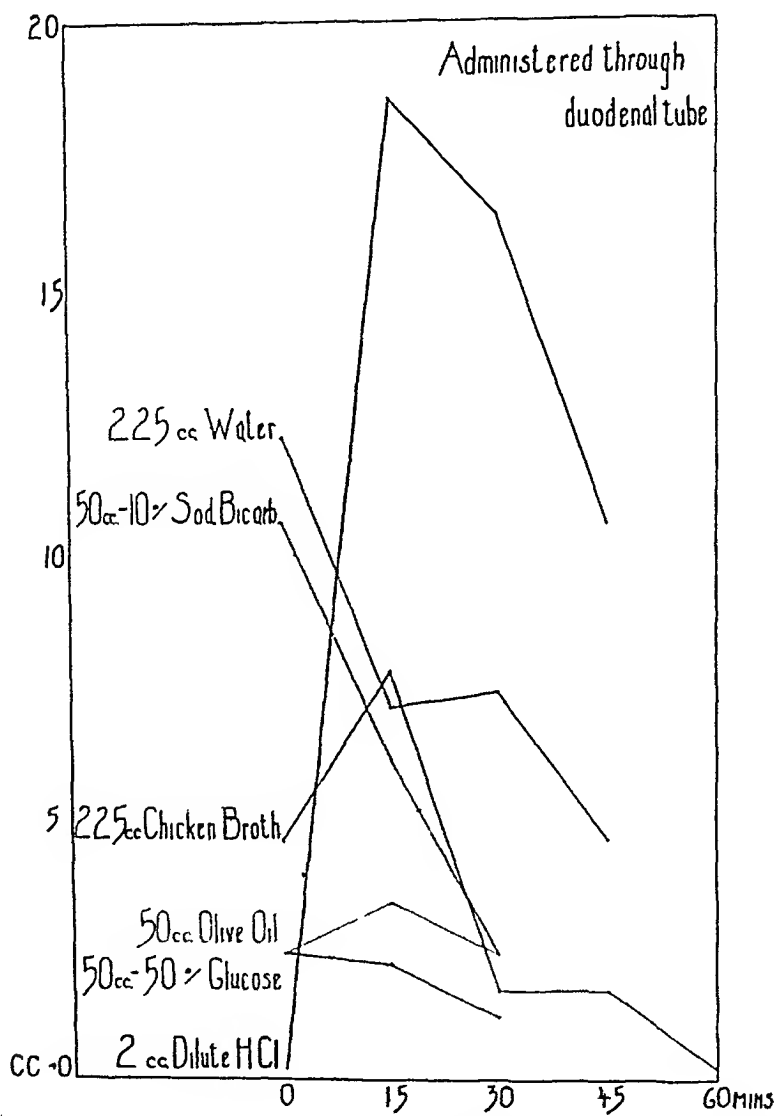


CHART 3—Substances whose influence upon pancreatic secretion were to be observed were introduced into the duodenum through the duodenal tube

*Chicken Broth*

Two hundred twenty-five cubic centimeters of chicken broth were introduced through the duodenal tube. The secretion rose from 4.6 cc to 7.8 cc, and then dropped, in successive 15-minute periods, to 1.7 cc, 1.7 cc and 0.2 cc. A moderate increase in flow resulted initially. It is known that meat extracts and protein derivatives in chyme exert a secretagogue effect. The stimulus provided an increase in pancreatic flow which was short-lived (Chart 3)

*Magnesium Sulphate*  
(Saturated Solution)

Fifty cubic centimeters of a saturated solution of magnesium sulphate was introduced into the duodenum through a duodenal tube. This was followed by a reduction of flow from 3.02 cc. in a 15-minute interval to 1.8 cc. of pancreatic secretion.

*Olive Oil*

Fifty cubic centimeters of olive oil was introduced into the duodenum through a duodenal tube. This was followed by a slight drop in external pancreatic secretion from 3.4 cc. in a 15-minute period to 2.4 cc. in a 15-minute period, without appreciable alteration in the determinations of chloride and bicarbonate contents in the secreted material.

These findings were contrary to those reported by McCaughan, Sinner and Sullivan,<sup>20</sup> in 1938, and by Comfort, Osterberg and Priestly,<sup>6</sup> in 1943.

Our conclusion from these results was that the introduction of olive oil into the duodenum produced no significant change either in the amount of pancreatic secretion or in the constituent electrolytes of the secretion (Chart 3).

*Glucose*

Fifty cubic centimeters of a 50 per cent solution of glucose was introduced into the duodenum through a duodenal tube. This was followed by a drop from 2.4 cc. in a 15-minute interval to 1.2 cc. of pancreatic secretion (Chart 3).

The second series of observations concerned themselves with the variations in flow through the fistula as a result of the *oral administration* of various substances (Chart 4).

*Water*

The result obtained with water administered by duodenal tube must be contrasted with that obtained when 225 cc. of warm water were given by mouth. Following this administration, we noted a slight rise from 23 cc. to 27 cc. and then a drop to 24 cc. in successive 15-minute periods. It is commonly recognized that water leaves the stomach almost immediately. In this instance, acid material was washed into the duodenum from the stomach with the water as a vehicle and consequently a rise in output resulted due to the lowered  $p_H$  of the duodenal contents (Chart 4).

*Sodium Bicarbonate*

Four grams of sodium bicarbonate given by mouth did not produce any appreciable effect upon volume flow of pancreatic secretion. The initial volume reading in a 15-minute interval was 24.2 cc. The subsequent readings at 15-minute intervals were 24.1 cc. and 22 cc. (Chart 4).

We concluded from this that sodium bicarbonate given in this quantity was insufficient to neutralize the stimulating effect of HCl upon the duodenal mucosa. The intubation experiment would indicate that repeated dosage with sodium bicarbonate would bring the  $p_H$  above the critical level of stimulation and would result in diminished secretion (See Chart 3). Prolonged administration of sodium bicarbonate was given in another of these

patients without appreciable change in carbon dioxide combining power  
Control blood determinations were made for carbon dioxide and chloride  
in the blood on July 12, 1943 Subsequently, 16 Gm of sodium bicarbonate

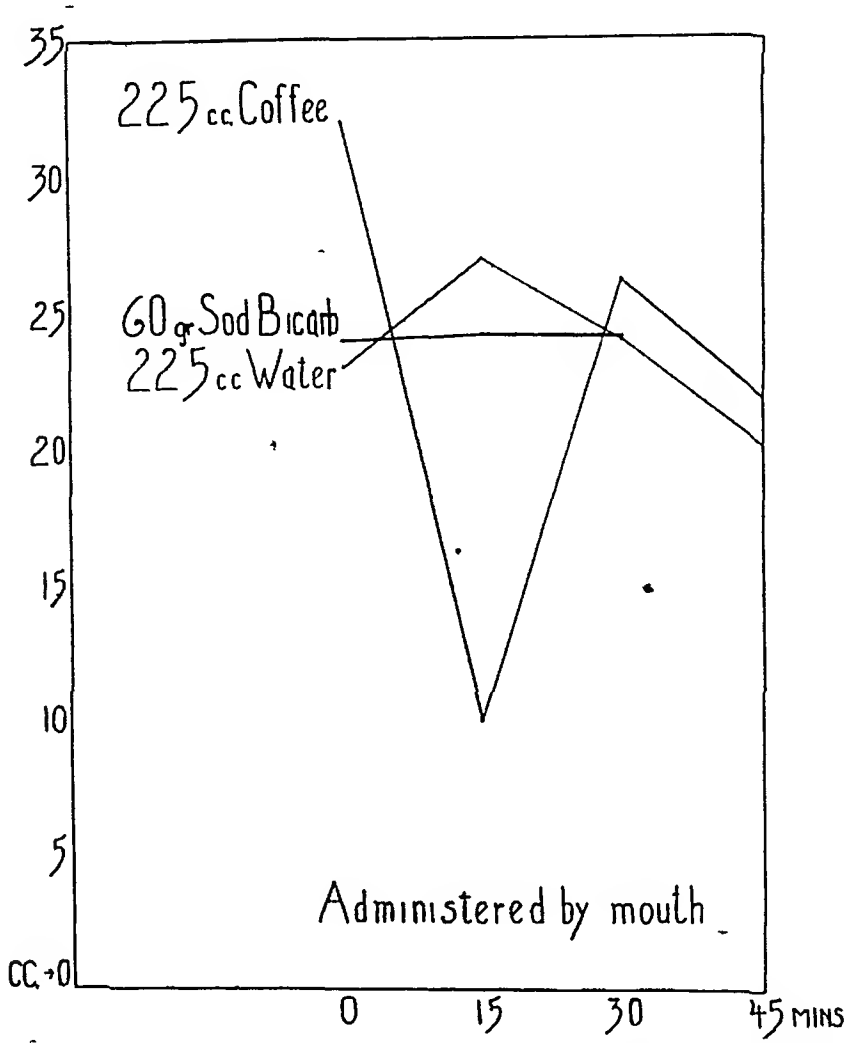


CHART 4—Substances whose influence upon pancreatic secretion were to be observed which were given by mouth

were given daily until a total dosage of 50 Gm was obtained Table VIII depicts the control and follow-up determinations

TABLE VIII

Date	Carbon Dioxide Combining Power	Chloride
Control (July 12 1943)	30 5	98 0
(July 14, 1943)	32 6	91 2
(July 15, 1943)	34 1	99 6
(July 16 1943)	35 0	101 2

Coffee

Two hundred twenty-five cubic centimeters of coffee given by mouth produced a drop in pancreatic secretion from a control standard of 32 cc in a 15-minute interval to 10 cc , to 26 2 cc and 21 8 cc (Chart 4)



### *Sulfanilamide*

The patient was given one gram of sulfanilamide by mouth, every 4 hours, for 12 doses. At the end of this time the concentration of the drug in the blood was 8.5 mg per cent—in pancreatic secretion 7.0 mg per cent. The first patient under similar therapy presented the following values: Blood—8.5 mg per cent, pancreatic secretion—9.1 mg per cent.

This afforded conclusive evidence that sulfanilamide was widely distributed throughout the pancreas, in concentration approximating that of its concentration in the blood, and that it is returned to the duodenum in pancreatic secretion in concentrations approximating that level obtained in the blood stream. This fact has been commented upon by other investigators.

### *Phenobarbital*

Previous investigators (Coffey, Koppanyi and Linger)<sup>4</sup> found that barbiturates given in large, hypnotic and anesthetic doses produced a reduction in gastric and pancreatic secretion, and that barbiturate was excreted in the pancreatic juice.

Following the administration of phenobarbital 0.1 Gm, readings were observed in volume of pancreatic secretion from a control normal in 15 minutes of 11.6 cc, to subsequent readings of 14.2 cc, 16.0 cc, 19.6 cc. This slight rise was not considered significant. Barbitol was not recovered from the secretion. These contradictory findings may have been due to the small dose of the drug employed.

### *Smoking (Cigarette)*

The patient under observation did not use tobacco in any form. He, however, agreed to smoke two cigarettes for us.

The base line of pancreatic secretion was at this time 24 cc in a 15-minute interval. Following smoking the volume of flow in the ensuing 15-minute interval was 20 cc and in the next 15 minutes returned to 24 cc (Chart 5).

Goodman and Gillman<sup>11</sup> state that the smoke of the average cigarette may yield 6–8 mg of nicotine. This diminution of volume flow was considered to be a nicotine effect. The diminution of secretion was accompanied by some sweating.

### THE EFFECT OF INTRAVENOUS FLUIDS UPON PANCREATIC SECRETION

The intravenous administration of 2,000 cc of physiologic saline in two hours and 21 minutes resulted in a marked increase in the rate of pancreatic secretion. The base rate of secretion prior to the administration of the saline was 30 cc in one hour. The average rate of secretion during the administration and for one hour subsequent to it was 60 cc (Table IX).

In a similar manner, 5 per cent glucose in physiologic saline was administered. The base rate was 45.2 cc per hour. The administration took 195

PHYSIOLOGY OF THE PANCREAS

minutes and the patient was observed for 225 minutes, during which time he secreted 255 cc of pancreatic juice His hourly rate of secretion was 60 cc (Table IX)

The secretory rate was increased markedly by augmented fluid intake There was no essential difference between the administration of physiologic saline and 5 per cent glucose in physiologic saline (Table IX)

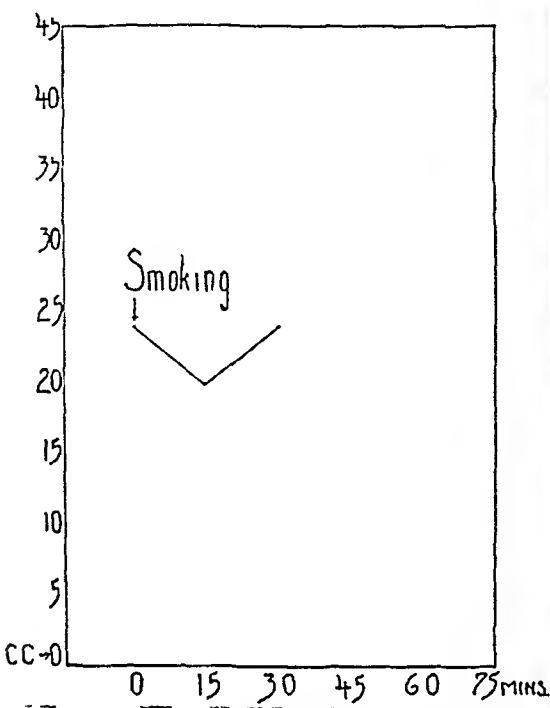


CHART 5—The effect of smoking on pancreatic secretion

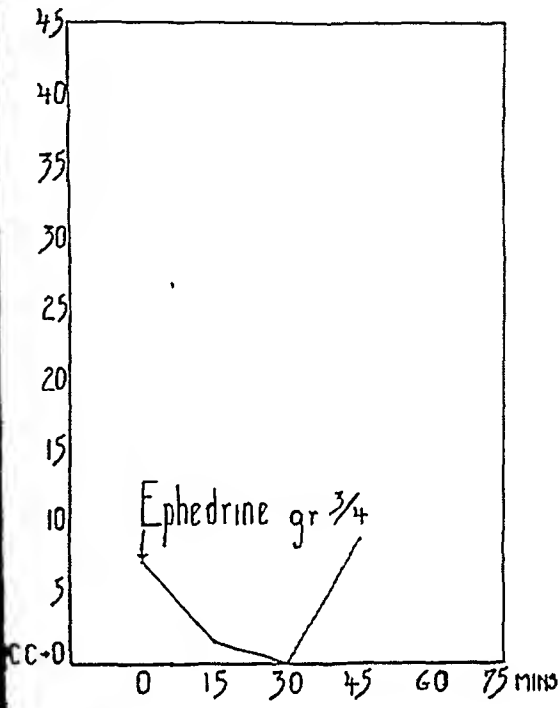


CHART 6

TABLE IX  
THE EFFECTS OF INTRAVENOUS ADMINISTRATION OF FLUID

Interval	Time	Saline I V	Pancreatic Inc Vol
60 mins	{ 12 00		20 0 cc
	1 00		
60 mins	2 00		24 0 cc
25 mins	{ 2 25 started		28 0 cc
39 mins	3 04	500 cc	51 0 cc
18 mins	3 22	500 cc	55 0 cc
48 mins	4 10	500 cc	61 2 cc
36 mins	4 46	500 cc	78 0 cc
	5 46		80 0 cc
	6 43		75 0 cc

5 PER CENT — GLUCOSE IN SALINE

60 mins	12 00		43 2 cc
	1 00		
60 mins	2 00		47 2 cc
	2 25		
71 mins	3 36	500 cc	60 0 cc
28 mins	4 04	500 cc	62 0 cc
43 mins	4 47	500 cc	48 8 cc
53 mins	5 40	500 cc	52 0 cc
	6 10		32 0 cc

OBSERVATIONS ON VOLUME FLOW ALTERATIONS INDUCED BY THE  
ADMINISTRATION OF DRUGS SUBCUTANEOUSLY*Ephedrine*

The intramuscular administration of 0.75 grain of ephedrine resulted in a marked inhibition of pancreatic secretion over a period of approximately 30 minutes, with a gradual return to normal at the end of 45 minutes. The diminution in flow was the result of a decrease in minute volume flow of blood through the pancreas, and this was due to the vasoconstrictor action of the drug. The concentration of chloride and bicarbonate in the pancreatic secretion showed a slight decrease from the preliminary control value.

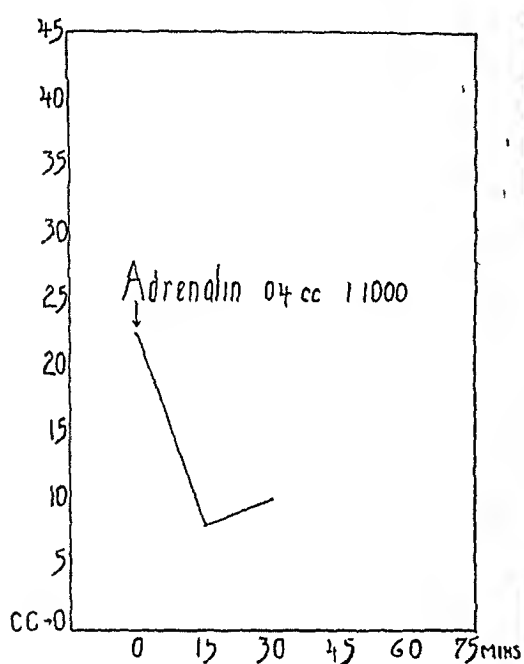


CHART 7

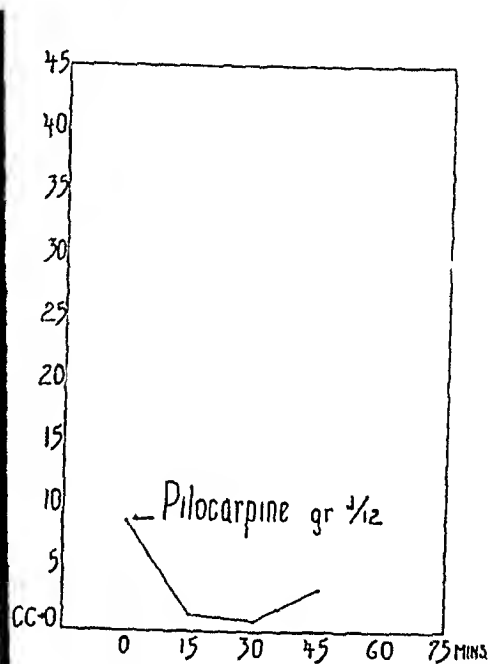


CHART 8

*Adrenalin*

The intramuscular injection of 0.4 cc of 1:1000 solution of adrenalin resulted in an abrupt diminution of pancreatic secretion, reaching its maximum effect in 15 minutes, after which a gradual increase in flow was noted. This diminution in flow was the result of the vasoconstrictor action of the drug, which produced a decrease in minute volume flow of blood through the pancreas.

*Pilocarpine*

The patient under study was given  $\frac{1}{12}$  gr of pilocarpine intramuscularly. This administration was made after a base-line of pancreatic flow had been established. The usual peripheral effects of the drug were soon observed. The result was dramatic. He had copious perspiration, marked salivation, the urge to defecate and urinate, his pupils were dilated, he was shaky and apprehensive. Pancreatic secretion dropped from 9 cc to 1 cc, to 1 cc,

## PHYSIOLOGY OF THE PANCREAS

to 35 cc , in successive 15-minute periods (This experiment was done three times with identical results ) There was a consistent drop of total bicarbonate concentration in the pancreatic juice, following the administration of pilocarpine

Pilocarpine produces its effect by a highly specific action on cells innervated by postganglionic cholinergic fibers This action is directly on the cholinergic substance (Goodman and Gillman<sup>11</sup>) The action should be the same as obtained on electrical stimulation of the vagus in the laboratory animal, yet a different result is obtained

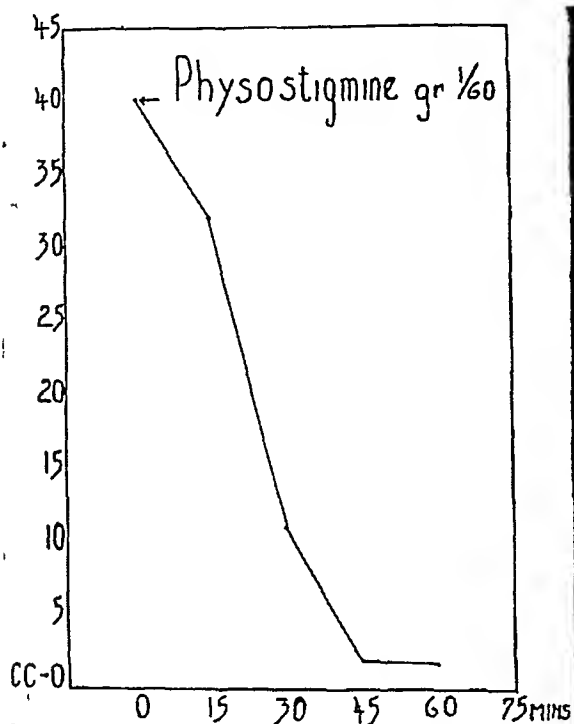


CHART 9

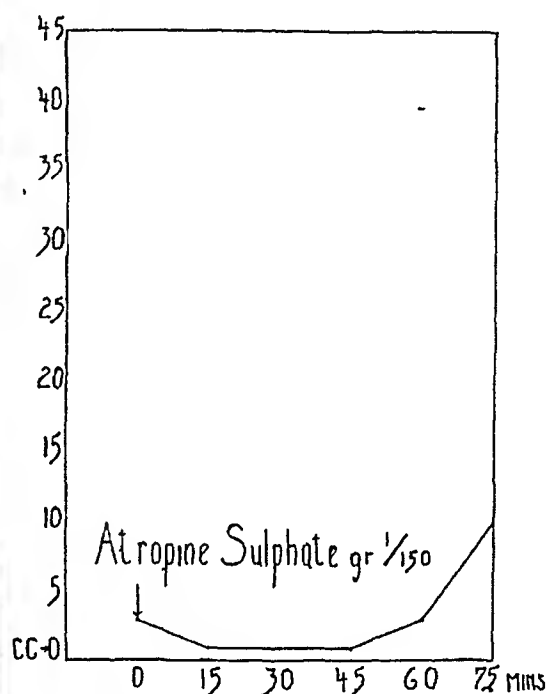


CHART 10

It would seem that where we had muscarinic stimulation on the pancreas plus increased flow of acid gastric juice providing an indirect stimulation (secretin mechanism), a combination of the two mechanisms would cause an increase in the production of pancreatic juice This did not occur, and, therefore, did not fulfill our expectations based upon the previously described action of pilocarpine

### *Physostigmine*

Some help in analyzing the deviation from the expected result after the administration of pilocarpine may be obtained from the following Physostigmine, grain  $\frac{1}{60}$ , was injected intramuscularly, and the flow in 15-minute periods was, successively, 40 0 cc , 32 cc , 11 2 cc , and 1 6 cc

It is known that physostigmine exerts its pharmacologic activity in the body by inhibiting cholinesterase in body fluids and tissues (Goodman and Gillman<sup>11</sup>) This esterase is responsible for the rapid and continuous destruction of acetylcholine Thus, physostigmine protects acetylcholine from enzymatic hydrolysis The responses obtained by the injection of physostigmine should

be the same as those from acetylcholine. It should be recalled that the presence of acetylcholine is necessary for the action of physostigmine.

It is also necessary to recall that acetylcholine produces both muscarinic and nicotinic effects. Acetylcholine is a mediator of nerve impulses, causing the secretion of epinephrine. Stewart and Rogoff<sup>24</sup> demonstrated this when they found that the epinephrine content of the blood increased to as much as fifteen times the normal after the administration of physostigmine. Thus, the reduction of flow from the administration of physostigmine is understandable. Epinephrine is released and by vasoconstriction diminishes the flow of blood through the substance of the pancreas, thereby reducing the flow of pancreatic juice. This occurs notwithstanding the fact that physostigmine by its muscarinic action should produce some increase in pancreatic flow.

Having considered the effect of physostigmine, it may be that pilocarpine has a mixed effect and produces both the muscarinic and some of the nicotinic effects of acetylcholine. Accordingly, it is suggested that epinephrine may be released when pilocarpine is injected and that the former causes the diminution in pancreatic output.

### *Atropine*

Atropine caused a definite decrease in the amount of pancreatic secretion in a very short time. Pancreatic secretion decreased from 18.4 cc to 1.8 cc, to 0.0 cc in 15-minute intervals.

Atropine produces a reduction of gastric motility and secretion, with an ensuing diminution in activation of prosecretin. Therefore, the principal effect is through an indirect mechanism (Farrell and Ivy<sup>9</sup>).

### *Morphine*

Morphine is a definite depressant upon pancreatic secretion. The effect is produced indirectly. The gastric secretion of hydrochloric acid is retarded. Gastric motility is lessened and the tone of the antral portion of the stomach is increased. The pyloric sphincter is contracted. The total effect causes a slowing in the passage of gastric content into the duodenum. The reduction in amount and the delay in passage of acid-gastric chyme into the duodenum results in the formation of a smaller amount of secretin, and, thus, the production of less pancreatic juice.

The patient was given 0.25 gr of morphine sulfate intramuscularly after a base line for secretion had been established. Flow dropped from 14 to 3 cc in a period of 15 minutes, with a gradual rise in the quantity of pancreatic juice secreted during the ensuing period.

### *Histamine*

The patient was given 1 cc of 1:1000 histamine phosphate subcutaneously after a base level of pancreatic secretion of 22.0 cc in 15 minutes had been established. Following this there was a fall to 12.5 cc in 15 minutes, after which the secretion rapidly increased to 28.0 cc, and subsequently to 40.0 cc in ensuing 15-minute intervals.

We have no explanation for the initial diminution of secretion. The

subsequent rise is due to the established action of histamine in increasing gastric acid secretion and increased gastric motility, with consequent stimulation to the secretin mechanism

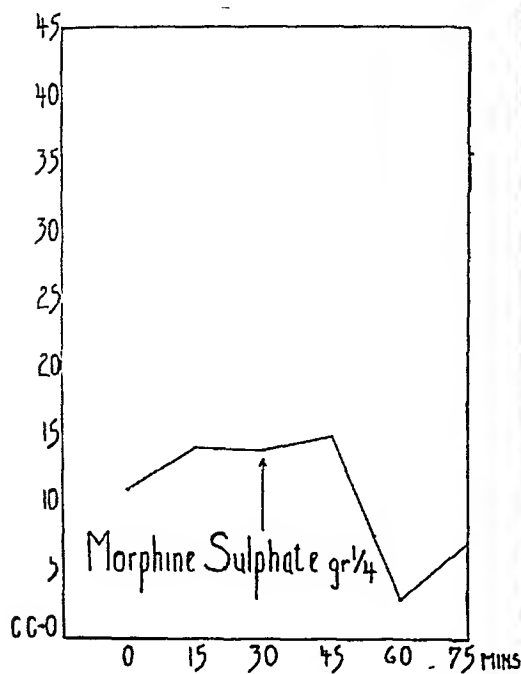


CHART 11

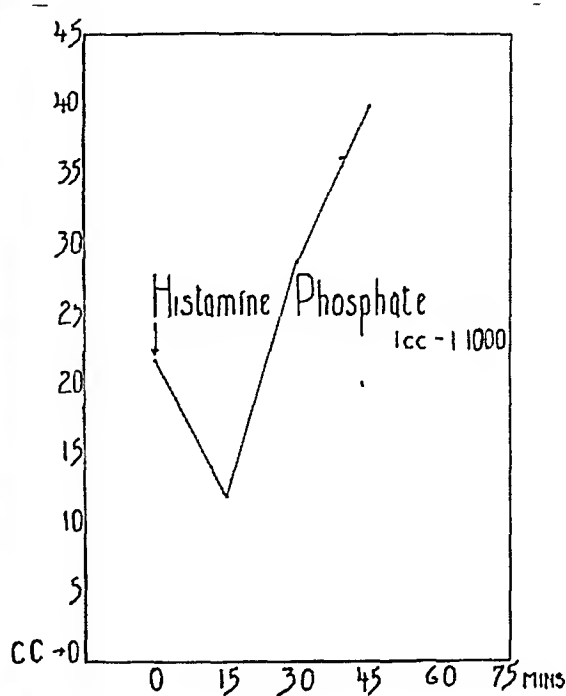


CHART 12

#### SUMMARY

1 Detailed observations upon three patients with external pancreatic fistulae have been presented. One of them produced 1770 cc in a 24-hour period.

2 Attention has been drawn to the marked alteration in water balance, plasma protein level and plasma electrolytes, with special emphasis upon plasma sodium in patients with severe external pancreatic fistula.

3 It has been emphasized in this presentation that the sodium loss in severe pancreatic fistulae produces a clinical syndrome similar to that described by Addison, with the exception that in these individuals adrenal disease is not present. This analogy has not been previously stressed.

4 The administration of adequate amounts of sodium and water in the presence of sufficient plasma protein to hold them in the circulation alleviates the symptoms peculiar to this syndrome.

5 Diminution in pancreatic secretion through the fistula may be obtained by the administration of a number of drugs. However, ephedrine and sodium bicarbonate are the most practical of these because of the unpleasant or deleterious side-effects of the others.

6 Detailed physiologic observations upon pancreatic function have been recorded. Certain of these observations contribute definite support to the theory that secretin secretion is a filtration process. These are:

- a Sodium ion is present in equal amounts in both blood plasma and pancreatic secretion.
- b The total of the concentrations of chloride and bicarbonate ions are the same in blood plasma and pancreatic secretion.

c The same amount of ionizable calcium is present in blood plasma and pancreatic secretion

d Sulfanilamide is found in the same amount in blood plasma and pancreatic secretion

7 Pancreatic flow is continuous throughout the 24-hour period, and is influenced, to great degree, by the state of hydration of the individual

8 Large amounts of ionizable calcium are normally returned to the gastrointestinal tract through pancreatic secretion. This phenomenon has not previously received the recognition it warrants

9 The appearance of sulfanilamide in therapeutic concentration in pancreatic secretion suggests its use in acute inflammatory disease of the pancreas

10 Pancreatic secretion is markedly stimulated by the administration of histamine intramuscularly, and by the intravenous administration of physiologic saline or 5 per cent glucose in physiologic saline, intravenously

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# THE HEALING OF SURFACE CUTANEOUS WOUNDS ITS ANALOGY WITH THE HEALING OF SUPERFICIAL BURNS\*

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INTEREST in the healing of cutaneous wounds produced by the removal of skin grafts was aroused by the fact that the wounds of superficial burns appeared to present a similar process of healing. Brown and McDowell<sup>1</sup> made the same observation, and later Cannon and Cope<sup>2</sup> used skin graft donor areas to test the effect of coagulants on epithelial growth.

Four hundred and sixty-nine skin graft donor areas were studied. These skin grafts were removed for use in plastic operations and for the covering of raw areas created by burns or trauma. Three types of skin grafts were employed: Thin Thiersch grafts and thicker split (intermediate) grafts which were removed with the Blair skin graft knife. Skin grafts of varying thickness (0.010–0.042 inches) were cut with Padgett's dermatome. The donor sites used were the medial aspect of the arm, the abdomen, the back and the thigh. A few grafts were removed from other regions of the body. The routine post-operative treatment of the donor areas was as follows: Gauze soaked in 1/1000 adrenaline solution and large saline packs were held with pressure against the bleeding donor area. Then strips of fine-meshed vaselined gauze, impregnated with sulfanilamide powder, were applied to the wound and covered by gauze, cotton and a pressure bandage firmly anchored by adhesive. The dressings over the skin graft donor areas were removed when the latter were healed. The approximate healing time of these donor areas was observed, the dressing being removed when the vaselined gauze could be easily detached from the new epithelial surface of the area. It is obvious that accurate comparative data are difficult to obtain because the thickness of the graft, which is cut with the dermatome, varies greatly with the thickness of the cement which is employed to produce adherence of the skin to the dermatome drum, because of individual variations in the characteristics of the skin of the different patients, and because of variations of the age and general condition of the patients. It is felt, however, that observations in a sufficient number of cases (469) have permitted us to formulate the following conclusions:

I. *The quality of the repair was roughly proportional to the rapidity of healing.*

Donor areas, healing in six to ten days, failed to leave more than a pink area, which rapidly became pale, leaving a faintly visible scar with a soft

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\* Sections of this paper were read by Dr. Converse before the Moynihan Surgical Club, July 26, 1942, Oxford, England.

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pliable base Donor areas, healing in 14 to 21 days, left a more visible, uneven scar with a harder base Some donor areas remained unhealed for a longer period, and often left retracted, hypertrophic scars

2 *The rapidity of healing appeared to be dependent upon a number of factors*

#### A *The Thickness of the Graft*

(1) After removal of thin Thiersch grafts at about the level AB in Fig 1 healing was achieved in six to ten days

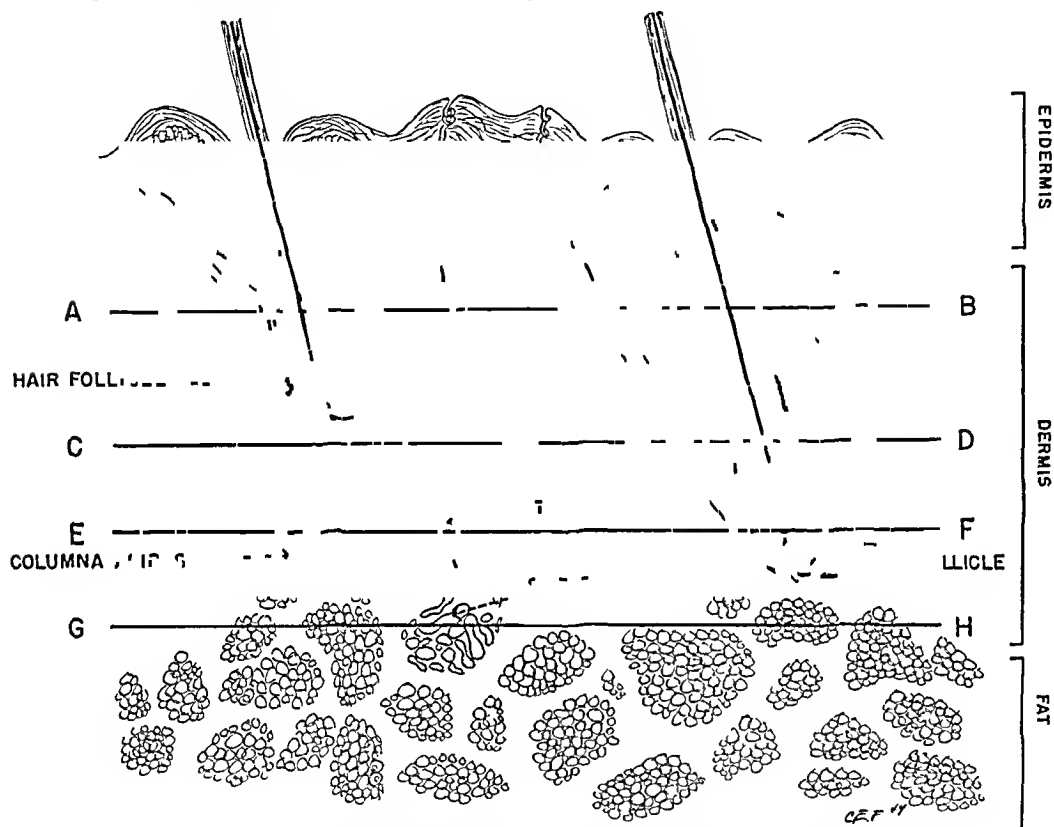


FIG 1.—Diagram of skin showing levels at which skin grafts are removed AB, level of a Thiersch graft, CD, level of an intermediate split graft EF, level of a thick graft, GH, level of a full thickness skin graft

(2) After removal of split (intermediate) grafts at about the level CD (Fig 1), healing occurred generally within 14 days

(3) When grafts were cut along the level EF, towards the base of the dermis, or along the level GH (Fig 1), at which lobes of fat began to appear, healing was much slower, taking from 21 to 58 days

#### B *The Thickness of the Skin of the Donor Site*

In four patients, 0.016-inch dermatome grafts were removed simultaneously from the abdomen and from the inner aspect of the thigh. The abdominal areas, in which the dermis is thicker, healed more quickly (average 12 days) than the thigh areas (average 16 days)

#### C *The Degree of Looseness of the Skin of the Donor Area*

In donor areas in which the skin is loosely bound-down to the underlying structures, healing occurred more rapidly by contraction

#### D *Infection*

## HEALING OF CUTANEOUS WOUNDS

In seven cases gross infection with suppuration were noted in the donor area. Cultures were not made. In each case, the dressing, maintained by a bandage, had slipped, failing to protect and immobilize the wound.

In six donor areas from which very thick grafts had been removed, infection was observed after the 23rd day. As a result of the infection,

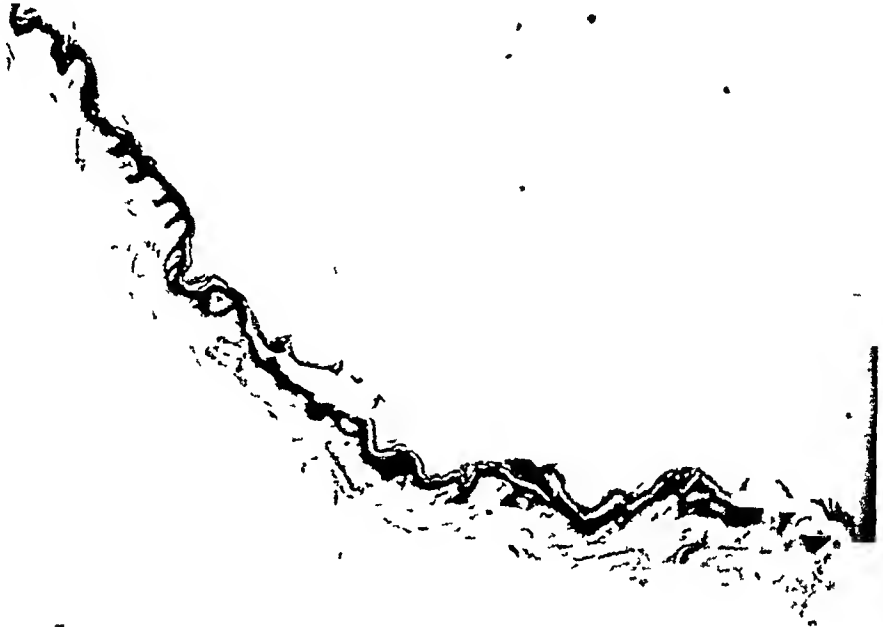


FIG. 2—Thin graft (0.25 mm—0.01 in.) removed from the abdomen (about 0.008 on the dermatome calibration) when fixed and embedded showing a portion of the dermis removed. HE  $\times 20$  (RISH 1585 (6) (42)).

necrosis of the remaining dermis was observed which resulted in sloughing followed by granulation of these areas. Healing occurred slowly (average healing time 52 days) leaving an hypertrophic, rough and contracted scar.

### PROCESS OF HEALING OF SKIN GRAFT DONOR AREAS

The process of healing of such areas was studied in four patients, who were undergoing a series of plastic operations, and who consented to the removal of biopsies from healing donor areas at various time intervals.

The healing of cutaneous wounds is a dual process, a combination of repair with contraction.

#### I *Process of Repair*

##### A *Source of Epithelium* (Figs 2-10)

The epidermis is removed with the skin graft so that the new epithelial surface must originate from the epithelial elements in the dermis (Figs 2-8), except from the edges of the defect where there will be regeneration from the surrounding normal epidermis attempting to cover the bare area

In the study of epithelial repair, histologic sections have revealed the following facts

- 1 In the healing of donor areas, the sebaceous glands participate, together with the hair follicles, in the reepithelization (Figs 3-7)

- 2 The hair follicles are the main source of epithelium (Figs 3-8)

- 3 The sweat ducts, running up from the sweat glands (which are situated in clusters at the base of the dermis between the lobes of fat), help to furnish epithelium when grafts are cut in the depth of the dermis. The sweat duct epithelium does not furnish as much epithelium as an occasional remaining hair follicle, and regeneration is much slower (Figs 9 and 10). It is to be noted that the hair follicles diminish in number as the deeper layers of the dermis are reached, as many hair follicles are implanted superficially. Horizontal sections through the dermis at different levels demonstrate this fact (Figs 11, 12 and 13)

This decrease in available epithelium can be demonstrated when cutting skin grafts with the dermatome at different levels. When a thin graft is cut, innumerable small bleeding points are seen. They are the transversely sectioned anastomotic vessels of the skin and are separated by areas of connective tissue containing a hair follicle (Fig 11). As thicker grafts are cut, the bleeding points become coarser and more widely spaced, and the hair follicles are also more widely separated. Near the base of the dermis, protrusions of fat appear, due to the irregular junction of the fat with the dermis (Fig 13). The junction between the dermis and the subcutaneous fat is not an even one. Numerous projections of fat, the "columnae adiposae" are seen, they join the base of the hair follicles, implanted at various levels in the dermis (Fig 1). The numerous islands of fat thus formed in the dermis facilitate contraction during the healing of dermal wounds.

It, thus, results that epithelization takes place from numerous islands of epithelium, which tend to join each other by cellular multiplication and migration. The more numerous these islands are, the more rapid the healing will be.

*B The formation of fibrous tissue and its influence on the quality of the epithelium*

Sections removed from donor areas which have healed rapidly (Fig 14), show a good quality epithelium over a thin layer of loose connective tissue. This layer is relatively avascular and elastic fibers do not develop until epithelial healing has been complete for some time. Even after five weeks, only very fine fibers are present (Figs 15, 16 and 17).

When healing has been slow, the appearance is quite different (Fig 18). Under a thin flat atrophic epithelium, under which there is little rete peg formation and presenting few or no hair follicles, is a thick layer of hori-

FIG 3

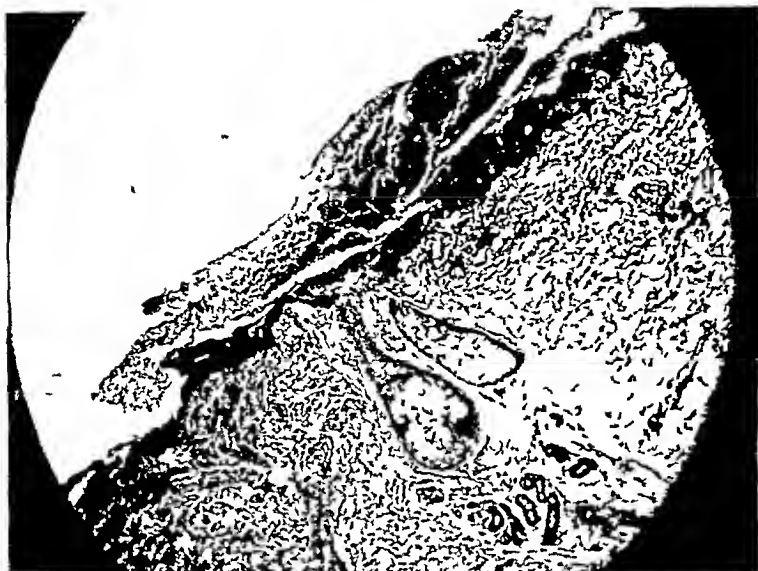


FIG 4



FIG 5

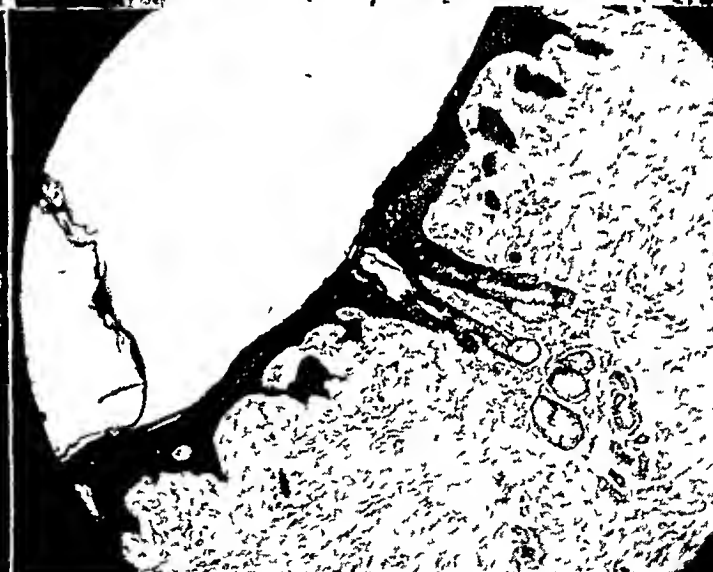


FIG 6

FIG 3—Donor area two days after removal of a thin graft showing commencing epithelial regeneration from the mouth of a hair follicle and from the sebaceous glands HE  $\times$  40 (RISH 1476 (4) (42)

FIG 4—Donor area three days after removal of a thin graft showing the epithelial sheet spreading out from a hair follicle HE  $\times$  40 (RISH 1606 (1) (42)

FIG 5—Donor area five days after removal of a thin graft Epithelial regeneration is complete, the epithelium is thicker than in Figure 4 There is a suggestion of rete peg formation and loose subepidermic connective tissue can be seen, particularly at the right hand end of the section HE  $\times$  40 (RISH 1606 (3) (42)

FIG 6—Donor area nine days after removal of a thin graft Epithelial regeneration is complete, the epithelium is much thicker than in Figures 4 and 5 There is keratinization and well marked though irregular rete pegs The newly formed loose subepidermic connective tissue is well shown HE  $\times$  40 (RISH 1476 (6) (42)

FIG 7



FIG 8

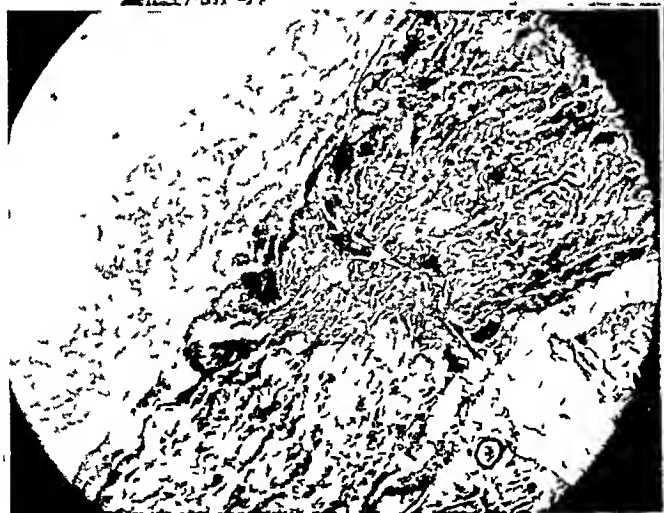


FIG 9

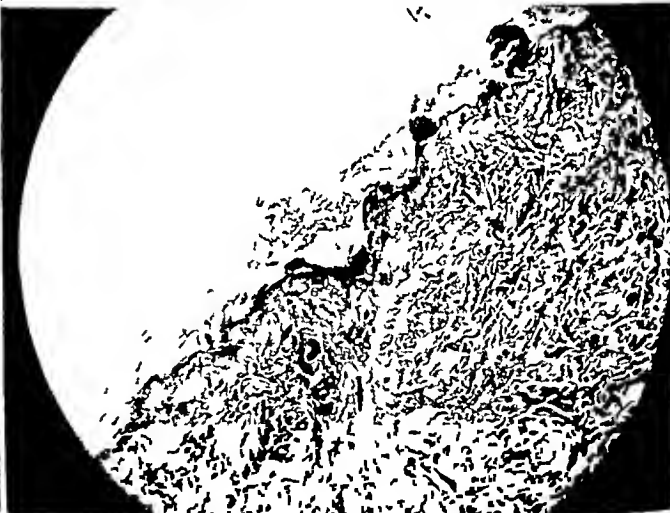


FIG 10

FIG 7—Comparison of healed donor area with an autograft after 12 days. Immediately after the thin graft had been removed a portion of it was reapplied and the rest of the donor area was allowed to heal. At the extreme right hand, a portion of the normal skin can be seen, then there is the area of regenerated epidermis with irregular rete pegs and loose subepidermic connective tissue, then a nodule where the regenerating epithelium has grown under the graft, then the autograft itself, and the granulating zone can just be made out. HE  $\times 75$  (RISH 1585 (1) (42))

FIG 8—Thick graft (1.36 mm, 0.05 in.) removed from abdomen (about 0.032 on dermatome calibration) when fixed and embedded showing the removal of the dermis and of the hair follicles. HE  $\times 20$  (RISH 1585 (5) (42))

FIG 9—Donor area three days after removal of a thick graft, only occasional minute islands of epithelium can be seen around the sweat ducts (Compare with Figure 4). HE  $\times 40$  (RISH 1606 (2) (42))

FIG 10—Donor area five days after removal of a thick graft, most of the donor area is bare and there is only a small island of epithelium arising in relation to a sweat duct (Compare with Figure 5). HE  $\times 40$  (RISH 1606 (4) (42))

zonally arranged collagen fibrils, completely deficient in elastica (Fig 19) and the whole dermis is poorly vascularized. These facts explain why these scarred areas present a hard base, why the epithelium is prone to fissure and ulcerate after trauma, and Brown<sup>3</sup> has also suggested that a factor in the liability to trauma is the lack of tethering of the epithelium due to the deficiency in rete pegs.

## 2 *Process of Contraction*

All healing wounds contract. Cutaneous wounds, such as donor areas, heal mostly by epithelization and little by contraction. Measurements of the degree of contraction of the wound after the removal of skin grafts were made by comparing (in 62 patients) the size of the piece of skin on the dermatome drum with the size of the healed donor area.

Very little contraction occurs (2-5 per cent) in the donor areas until very thick grafts are removed. Contraction increases to (5-10 per cent) and may reach as high as 20 per cent when the grafts are cut in the base of the dermis where fat begins to appear.

Infection and mechanical and chemical irritation delay epithelial healing, and contraction is increased. We have already noted that contraction occurs more readily when the skin of the donor area is loosely bound down to the underlying tissues. This contraction of the wound is most marked along the direction of the lines of the skin (Langer's lines).

## CONCLUSIONS

### THE "INTER-ISLAND CONTRACTION"

It would appear that epithelial resurfacing originates from the individual epithelial islands formed from each hair follicle, sweat duct or cluster of sweat glands. Each epithelial island endeavors to join its neighbors not only by cellular division and migration but also by contraction (inter-island contraction). The longer epithelial healing takes to resurface the wound, the more marked this inter-island contraction will be. Such a delay in healing was observed in donor areas, in which the dermis was transected near its base, this was apparently due to the diminution in the number of elements of available epithelium, but infection, and mechanical and chemical irritation produce the same retarding effect. In such cases, a thick layer of relatively avascular inelastic fibrous tissue is laid down which is covered by an atrophic epithelium of poor quality (Figs 18 and 19).

## HEALING OF SUPERFICIAL BURNS

In the past there has been a tendency to attribute success or failure of local burn treatment to the type of treatment used. According to some, the use of certain chemicals over the burn wound has resulted in "healing without scars" of burns. It is true that the necessity of treating the burn with full-thickness skin loss, by early skin grafting is now generally recognized. However, it would appear that within the group of burns generally classified as second degree burns, variations in the quality of the healing of these areas depend upon the extent of the tissue destruction.

FIG 11

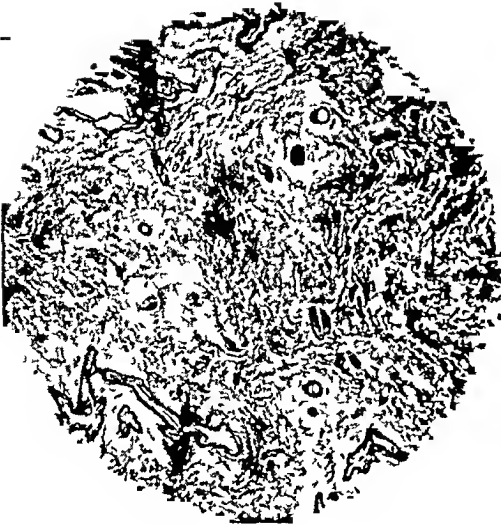


FIG 12



FIG 13



FIG 14

FIG 11—Horizontal section of skin of thigh below the epidermic surface, cut 0.18 mm (about 0.007 in. on the dermatome calibration) when fixed and embedded. The openings of the hair and sweat glands can be seen, also a portion of the epithelium where the deeper epithelial folds occur. HE  $\times 20$  (RIPM 345/43)

FIG 12—Horizontal section of skin of thigh, below the epidermic surface, cut 0.36 mm (about 0.028 in. by the dermatome calibration) when fixed and embedded. There are no hair follicles and the sweat ducts can only be made out with difficulty and are scanty. HE  $\times 20$  (RIPM 345/43)

FIG 13—Horizontal section of skin of thigh, below the epidermic surface, (about 0.034 in. by the dermatome calibration) when fixed and embedded. The coiled sweat glands are seen as well as intradermic protrusions of fat. HE  $\times 20$  (RIPM 345/43)

FIG 14—Healed donor area 32 days after the removal of a thin graft. The epidermis is keratinized and of moderate thickness. Rete pegs are not marked but there is the normal undulation of the skin, and hair follicles. The contrast between the new formed subepidermic connective tissue which is becoming collagenized and the coarse collagen fibers of the original dermis can be clearly seen. (Compare Figures 6 and 18). HE  $\times 40$  (RISH 1476 (3) (42))

During two years' service at the American Hospital in Britain (1940-1942) 191 burns were observed. These burns were seen at all stages, some as early as two hours after injury, others after complete healing, often because of the need for secondary plastic operations. The youngest patient was age 5 the oldest, 64. The patients were civilians as well as belonging to the Armed Services. The causes of the burns were variable, 143 were related to the War (gasoline explosions, plane crashes, incendiary bombs, flash burns of high explosives, accidents in war industries), 48 were of the usual civilian type. Early treatment had often been carried out in other hospitals, and the methods of local treatment employed were very variable: irrigation methods (saline baths, irrigation envelopes), coagulation methods (tannic acid and silver nitrate, gentian violet, triple dye, sulfadiazine in triethylanolamine), lightly applied dressings of wide-mesh vaselined gauze (*tulle gras*) and moist saline dressings, pressure dressings with fine-mesh vaselined gauze, plaster encasements and splints. The healing of these burn wounds was observed, and 63 biopsy specimens were removed for histologic examination.

In defining the depth of the burn, it would seem more logical to use anatomic terms. Table I shows the terminology used in this paper.

TABLE I

CLASSIFICATION OF BURNS

Superficial Burns (partial skin loss)	<i>Epidermal burns</i> Erythema	}	Heal well
	Epithelial desquamation		
	<i>Dermal burns</i> Blistering	}	Heal slowly, with contraction; may require skin grafting
	Destruction of superficial layers of the dermis		
Deep Burns (total skin loss)	<i>Deep dermal burns</i> Destruction of the dermis down to the deep layers		
	<i>Mixed burns</i> Small areas of total skin loss alternate with areas of deep dermal burns	}	Heal with difficulty, producing contractions and deformities. Skin-grafting the rule
	Destruction of the whole-thickness of the skin into, or beyond, the fat		

1. *Epidermal Burns*—These burns are characterized by erythema, often followed by an epithelial desquamation. A detailed study of the early histologic changes in experimental burns has been made by Leach<sup>4</sup> and exactly comparable changes have been observed in man.

2. *Dermal Burns*—Blistering is the rule. In the histologic sections studied, blisters were due to an epidermo-dermal separation produced by the exudation of fluid. In one section, the layer of separation was deeper than the junction of epidermis and dermis, in the dermis itself.

When the base of the blister is red, smooth and moist, healing may be expected in the absence of infection in 7-10 days. Epithelization in such superficial burns originates, possibly from a few remaining islands of basal epithelium, and from the hair follicles and the sweat ducts. The histologic picture is the same as that observed in the healing of a donor area after the removal of a thin skin graft (Figs 3-6 and 14-17).

When the base of the blister is grey and dry, the dermis is more deeply involved, and healing will be slower because a layer of burned dermis must first be eliminated as a slough. Histologic examination has shown that



FIG 15



FIG 16



FIG 17



FIG 18

FIG 15 —Normal skin to show elastic fibers. There is an imperceptible transition from the coarse fibers of the dermis to the fine fibers of the subepidermic region. Orcein  $\times 120$  (RISH 1585 (1) (42))

FIG 16 —Healed donor area 12 days after removal of a thin graft from the abdomen (0.008 in. by the dermatome calibration). The elastic fibers of the original dermis can be clearly seen, but no elastic fibers have developed in the newly formed, subepidermic loose connective tissue. Orcein  $\times 120$  (RISH 1585 (1) (42))

FIG 17 —Healed donor 32 days after removal of a thin graft from the abdomen (0.008 in. by the dermatome calibration). The elastic fibers of the original dermis can be clearly seen and very fine elastic fibers have developed in the new formed subepidermic connective tissue. (Compare with Figures 14, 16) Orcein  $\times 120$  (RISH 1476 (3) (42))

FIG 18 —Healed hypertrophic scarred donor area 65 days after removal of a thick graft from the abdomen (about 0.034 in. by the dermatome calibration). There is a layer of atrophic epidermis with no formation of rete pegs and absence of hair follicles though sweat glands are present. The newly formed subepidermic connective tissue has become collagenized, but deep to it are bundles of horizontally arranged closely knit collagen fibers. The original dermis can just be made out at the bottom of the photomicrograph. HE  $\times 40$  (RISH 1476 (2) (42))

although the structural pattern of the dermis has been maintained, yet the physicochemical characters of the collagen have been profoundly altered.

3 *Deep' Dermal Burns*—A thicker layer of dermis is destroyed, exposing the base of the dermis which appears as grossly punctated. Often one may see numerous small islands of epithelium, resembling minute pinch-grafts



FIG 19—Healed hypertrophic scarred donor area 65 days after removal of a thick graft from the abdomen (about 0.034 in. by the dermatome calibration). The elastica of the original dermis can be seen, but there is virtually no elastica in the newly formed subepidermic connective tissue or the underlying collagen bundles. Note the thickness of the newly formed tissue (1.6 mm, 0.066 in.), whereas, in a healed donor area, after removal of a thin graft, the new formed connective tissue is only 0.36 mm (0.013-in.) thick. Orcein  $\times 20$  (RISH 1476 (2) (42)). (Compare with Figure 17)

from which epithelization spreads as a pearly-white thin layer. Healing is prolonged, particularly in infected cases. The healed epithelium is often thin, parchment-like and prone to cracking. Histologic examination in the healed stage shows an appearance similar to that described in a healed deep donor area, save that the zone of horizontal collagen fibrils is greater (Figs 18 and 19)

## CONCLUSIONS

### SKIN GRAFTING AFTER SUPERFICIAL BURNS

In superficial burns when the deeper layers of the dermis are involved, (deep dermal burns, mixed burns) healing occurs with considerable contraction (inter-island contraction). Although the burn has not caused destruction of the full-thickness of the skin, a loss of skin surface is noted (invisible loss). This contraction and loss of skin surface following superficial burns is noted particularly

1 When the skin of the area is loosely attached to the underlying structures, *e g*, the skin of the dorsum of the hand, or of the eyelids (resulting in ectropion)

2 In the vicinity of joints where it tends to interfere with their normal function

The newly healed skin is smooth, shiny and very tight, it is often keloidal. Avascular and inelastic scar tissue is the enemy of serviceable repair. Without minimizing the value of massage, ointments and other physical therapy methods, too much time may be wasted in the rehabilitation of patients following superficial burns by their use, particularly in burns of the hands. Roentgenotherapy may be useful to reduce and soften hypertrophic scars, but if scar-epithelium overlies scarred dermis, the best treatment is their complete replacement by thick skin grafts. The presence of a thick dermal pad under the epithelium has been the reason for the serviceable repair given by the split graft.

Skin grafting is indicated in superficial burns for two main reasons.

1 For the relief of skin deficiency, of tightness, following inter-island contraction of deep dermal and mixed burns, particularly on the dorsum of the hand, around joints, for ectropion of the lids or distortion of the features of the face.

2 To replace skin of poor quality. Thin, shiny or keloidal skin is poorly resistant to every day trauma. It tends to crack and ulcerate, even as a result of cold weather. Return of sensation is poor, and the appearance of the skin is often disfiguring.

#### SUMMARY

1 In the study of superficial burns, a comparative study of 500 donor areas of partial thickness skin grafts were done. The following facts were noted:

- 1 The quality of the repair was roughly proportional to the rapidity of healing.
- 2 The rapidity of healing was dependent upon
  - A The thickness of the graft removed
  - B The thickness of the skin of the donor site
  - C The presence or absence of infection
- 3 Epithelial healing originates from the epithelial elements in the dermis, hair follicles, sebaceous glands, sweat ducts. The number of these elements decreases in depth of the dermis and so healing is slow.
- 4 In slow-healing areas, abnormal fibrous tissue is laid down in excessive amounts. The epithelium formed is of poor quality.
- 5 Contraction following healing is appreciable in areas from which grafts have been cut near the base of the dermis. In deep dermal burns and in mixed burns, such a contraction has been observed and is called "inter-island contraction."

2 From 191 burned patients, 63 biopsy specimens were removed. The extent of the anatomic destruction of the burn wounds and the mode of healing of these wounds were observed.

3 An anatomic classification of burns is proposed.

4 A description of the clinical and pathologic aspects of superficial burns is given.

5 The need for skin grafting certain superficial burns because of the tightness produced as a result of inter-island contraction or because of the poor quality of the healed skin is noted.

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## BATTLE CASUALTIES IN A SOUTH PACIFIC EVACUATION HOSPITAL

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WARFARE in the South Pacific involving island to island moves has presented difficult problems in the care of the wounded. Our experience with battle casualties has been far different than we anticipated. Instead of treating fresh wounds, we have had to deal primarily with wounds in which infection was well established upon admission to the hospital. I hasten to comment that this was unavoidable. In spite of a well planned South Pacific surgical program, it was too often impossible to bring wounded soldiers to hospital facilities before the golden six- to eight-hour period following injury had passed. Men were frequently wounded at night and could not be removed from their fox holes before dawn. Then their transportation through jungle and over impassable roads was time-consuming. The best that could be done—and in general it was well done—was to stop hemorrhage, put sulfa drugs in the wounds, apply simple dressings, support fractured extremities with splints and evacuate. This had to be accomplished first by small boat and then by air. The majority of the patients were received at this hospital from two to five days after injury. Some had had further treatment before arriving. The seriously wounded had received blood transfusions but plasma was the mainstay of support in the forward area. In the care and study of these patients a few points of interest presented themselves, and the importance of applying the established fundamental principles of wound treatment was reemphasized.

*Gas Gangrene*—In the battle casualties received at this hospital there has been no case of classical gas gangrene. This, of course, may be coincidence, since unquestioned cases of gas gangrene have been reported at other hospitals in this area. Small amounts of air bubbling from an infected wound does not necessarily mean gas gangrene in the ordinarily accepted sense of a death-dealing, spreading infection requiring prompt and heroic treatment. Great caution is advised. We have had five patients with severe wounds, grossly infected, from which gas bubbles exuded and about which slight crackling could be palpated. Because the well-recognized clinical picture of gas gangrene, with severe pain, rapid pulse, relatively low temperature, marked local edema, coppery discoloration of the skin and overwhelming toxicity was absent, we, with considerable trepidation, treated the patients conservatively, in immobilization. Large doses of polyvalent gas gangrene serum were given intravenously. Cultures from the wounds yielded gram-positive, spore-forming anaerobes resembling *C. welchii*. Facilities for virulence tests were not available. Since it is well recognized that many patients whose wounds harbor the Welch bacillus do not develop clinical gas gangrene, positive cultures do not warrant amputation or other types

of radical surgery unless the clinical picture supports the laboratory findings. All these patients made an uneventful recovery.

A second group of battle casualties who have air in their tissues, exclusive of chest injuries, and who demand careful differentiation, are those in whom air has been sucked into the tissues by penetrating or perforating missiles. This observation has not been sufficiently stressed in the surgical literature of war. In these patients, clinical examination reveals, to the palpating hand, typical crackling in the tissues but roentgenologic examination shows that collections of air lie along the course of the missile rather than in the planes of the tissues, as in gas gangrene. Furthermore, in the former, the trapped air shows on the roentgenogram as irregular-sized, large and small dark splotches, whereas, in the latter group, the gas is frequently represented by small, dark, oval areas lying in parallel rows.

Our first patient presenting this picture had sustained a wound of his right forearm three days before admission. The shell fragment had entered just above the wrist and, without producing bone injury, had torn through the extensors of the forearm and lodged about one inch above the elbow at the lateral surface of the humerus. His wound was mildly infected at the point of entrance. There was crackling in the tissues all along the course of the shell fragment, and roentgenologic examination revealed blobs of air in the tissue along the tract. The patient did not appear acutely ill, his temperature was 101° F. Because of uncertainty and inexperience, we laid open the tract but found the muscles free from any of the changes so typical of gas gangrene. The wound was packed open with vaselined gauze and a circular plaster encasement applied. Within three weeks, the wound was covered with healthy granulation tissue, allowing a successful secondary closure. We were in error—misguided by the presence of air in the tissues. This condition has been observed and recognized frequently since.

These two groups of patients require most careful and thoughtful observation. Evaluation of air in the tissues of severely wounded extremities or gas formed by microbic action in and about grossly infected wounds is of paramount importance. To delay treatment in the presence of classical gas gangrene is inexcusable—to amputate unnecessarily is tragic.

*Infections*—Infection was well established in practically every battle wound when it came under our care. Knife, machete and bayonet wounds, and perforating wounds of soft tissue caused by machine gun bullets were occasionally clean. The extensive wounds were dirty, foul-smelling, and covered with pus and bits of sloughing tissue. Yet, interestingly, there was but one patient in the entire group who had an overwhelming infection, with symptoms of profound toxemia. That is unique because accidental wounds in civilian life are not infrequently followed by severe infections. Cultures from these infected wounds, while unsatisfactory because of the presence of large amounts of sulfanilamide, yielded a variety of organisms—anaerobes, staphylococci, albus and aureus, hemolytic and nonhemolytic, gram-negative bacilli and a few nonhemolytic streptococci. Hemolytic streptococci were

found only once in 25 cases studied bacteriologically. Whether the sulfa drugs in the wounds kill these streptococci or whether the low incidence of upper respiratory infections in this theater of war accounts for the infrequency, is a matter of conjecture. Coincidence may play a rôle. The ironclad rule of wearing caps, sterile gloves and masks covering mouth and nose when treating wounds may be a factor.

The low incidence of infection in potentially clean operative wounds has surprised us, as we were under the impression that wounds would not heal kindly because of the excessive perspiration in the heat and humidity of the tropics. The contrary has been true. In potentially clean operative wounds, we have had infections, with an incidence of two per cent. In 120 consecutive herniae, repaired with silk throughout, there was one post-operative wound infection.

*Treatment of Infected Wounds*—The pathology of an infected wound and the physiologic processes involved in its healing have not changed. Often the fundamental principles have been obscured by the host of accepted and discarded lotions, chemicals, salves, washes, irrigants, digestants and wound-healing potions of all kinds. A few make the wounds look better and smell better—that's all. In every infected wound, from a scratch to an extensive avulsion of the muscles of the thigh, there eventually forms, if the patient survives, a barricade between healthy and infected tissue. This wall, or pyogenic membrane, is nature's mechanism of defense against the invasive forces of infection. Anything that enhances its formation is desirable, anything that injures or weakens it is a menace. Each break in that wall, made by instrument or rough handling or "cleaning," is an avenue for bacterial invasion and must be closed by a repetition of the reparative process.

Towards the early, unimpeded and effective building of this wall of defense, all of our energies must be directed. Ever since the Napoleonic wars, astute observers have noted the importance of wound rest, but to Orr rightly goes the credit for popularizing the principles and mechanism of its accomplishment.

*Procedure*—An infected, extensive, soft-tissue wound is treated the same as an infected compound fracture, except that in the latter group the fragments are aligned in the best possible position. The mechanism of reduction, alignment and fixation with pins or twin pin units or traction is not within the scope of this paper.

All patients with severe, infected wounds, with or without fracture, are brought to the operating room, where surgical staff and attendants are capped and masked. The dressings are removed with sterile instruments and the wound inspected. The time for débridement has forever passed after infection is established, nor can such a wound be "cleaned" by any process devised by man. Only obviously dead tissue is cut away, and any attempt to cut away live but infected tissue will lead to disaster. If there are pus pockets, they are gently opened. Large foreign bodies, easily available, are lifted out, but during the acute stage of infection there is no digging for missiles.

or shell fragments That can be done after the infection has burned itself out and local as well as general immunity has been established Washing or sponging, if done, is so gentle that bleeding is not started The wound is filled, not stuffed, with gauze so thoroughly impregnated with vaseline that it will serve as a nonadherent drain and not as a plug No rubber drains of any kind are used A voluminous dressing of fluff-gauze is laid on and about the wound and covered snugly with a liberal amount of sheet wadding Over this a circular plaster encasement is applied Because of the excessive humidity in the tropics, it is necessary to make the plaster encasement twice as thick as one would at home

Wounds of the shoulder and hip are enclosed in plaster spicas, wounds about the knee are protected by leg encasements from groin to toes, wounds about the elbow require encasements from shoulder to fingers Immobilization is the objective, and it must be complete

The patient is returned to his ward where his wounds are safe from prying eyes and from fond but meddlesome fingers Along with rest to the wound and consequent relief from pain come physical and mental relaxation so important in the treatment of any disease Sulfa drugs by mouth are continued as indicated Blood and plasma transfusions are used freely as needed

The patient's temperature will go up as a result of the minor manipulations of a change of dressing and the application of an encasement A return to normal may be expected within a few days If the temperature fails to drop in the morning, indicating sealed-up infection, a change of the encasement and a review of the wound is indicated Excessive drainage and soaking, also, necessitates a change of the encasement We rarely cut windows in them If the odor becomes too offensive, the encasement is changed, however, a smelly encasement is largely a matter of mental attitude

*Anesthesia*—Ether administered by the open-drop method is not practical in the tropics because of the high humidity Practically all cases given ether were induced with nitrous oxide-oxygen and maintained with ether-oxygen administered by the closed absorption technic

Pentothal sodium, alone or combined with nitrous oxide-oxygen, was found to be the anesthesia of choice for most battle casualties

Basal anesthesia, consisting of nembutal, morphine and scapolomine, was adequate for many casualties requiring merely a dressing and change of the encasement or minor manipulation of fractures

Spinal anesthesia was not used for battle casualties Other methods were considered safer

Based on these experiences, there are a few "do's" and "don'ts" that are very elemental but seem to require constant reiteration

- 1 Record, record, record
- 2 Especially in case of upper extremity injuries Is the radial pulse present, are the nerves intact, are the tendons severed? Make a record
- 3 Do not close battle wounds



- 4 Dry gauze packed in wounds acts as a plug—use only when absolutely necessary for control of hemorrhage
- 5 Immobilize adequately Do not use unpadded encasements on patients who are to be removed from your own continuous personal observation
- 6 Do not use rubber drains—never in the region of large vessels Gauze, *thoroughly* impregnated with vaseline, properly placed, will allow for adequate drainage Do not pull strips of vaselined gauze through perforating wounds
- 7 Roentgenograms and records are frequently lost or do not accompany the patient, therefore, with indelible pencil, write on the encasement Date of injury, date of application, draw position of fragments in all fractures, indicate wound of entrance and wound of exit with a circle the size of the wound and write in the circle, "vaselined gauze"

#### CONCLUSIONS

Our results with this simple regimen have been Patients who eat well, sleep well and are happy because they are free from pain Their wounds clean themselves without interference and become covered rapidly with healthy granulation tissue

# URINARY COMPLICATIONS OF PELVIC ENDOMETRIOSIS

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SECONDARY ENDOMETRIOSIS of the urinary organs is a relatively unusual complication, although the condition has been recognized for some years. The urinary tract may be invaded in any part of its length below the junction of the middle and lower third of the ureters. The disease may be localized to any single part of this tract or it may, by progressive advance, involve all the structures below the brim of the pelvis. In the cases herewith cited are (1) two instances of diffuse stromatous secondary endometriosis, involving the whole urinary tract below the brim of the pelvis, causing occlusion of both ureters and leading to complete destruction of the kidneys and death, owing to uremic coma, (2) there are also two other instances of secondary invasion of a single ureter by transperitoneal penetration, leading to destruction of the kidney on that side, and (3) one instance of secondary urethral endometriosis.

The symptomatology varies considerably in different cases due to several factors. (1) The site of the urinary implantation, (2) the cellular structure from which the disease originated, which (3) determines whether the endometriosis present in the urinary tract responds to the monthly cycle or not. These main factors will be emphasized in their appropriate sections.

In the author's monograph, "A Study of Endometriosis," it was emphasized that all cases of endometriosis originate in the endometrium. The endometrium is made up of two specific cellular structures—the stromal cell and the lining cell of the uterine secretory glands. Endometrial ectopias may be made up wholly of (1) the stromal cells, simulating sarcomatous disease which are, therefore, designated as stromatous endometriosis, or (2) the ectopias may be composed of glands and stroma and, therefore, may be termed mixed endometriosis. It was further emphasized that only the superficial layers of the endometrium respond to the monthly cycle, whereas, the deeper layers are not appreciably affected. For this reason, endometrial cells from the superficial layers may retain their capacity for cyclical response when they implant in ectopic position, whereas, the deeper, nonresponsive cells are resistant to monthly cyclical influences when in ectopic position.

It can readily be seen that there are three modes of invasion of the urinary tract by endometrial tissue. (1) Direct, by lymphatic continuity or back-flow from the deep uterine mucosa through the uterine wall into the muscularis and mucosa of the bladder, (2) indirect, from implants in the peritoneal vesico-uterine pouch and thence into the muscularis and mucosa of the bladder, and (3) traumatic displacement, with implantation on the peritoneal surface of the bladder following surgical intervention in any case of endometriosis. From these sources of transmission it follows that Group I

invasions affect chiefly the trigone and base of the bladder, where there is direct lymphatic continuity with the uterus, while Group II and III invasions affect chiefly the fundus of the bladder. It is to be noted that the endometrial tissue in Group I cases arises from the deep uterine mucosa and is not responsive to the uterine cycle. The same is not true of the endometrial tissue aggregates in Groups II and III. These are chiefly instances of peritoneal implants or traumatic transplants resulting from "spill" and are primarily derived from the responsive superficial portion of the endometrium. These factors determine the presence or absence of the chief diagnostic sign due to endometriosis of the urinary tract, namely, cyclic urinary hemorrhage.

#### SECONDARY URETHRAL ENDOMETRIOSIS

To the best of my knowledge there are no recorded cases of secondary urethral endometriosis. One case came under my observation some seven years ago.

**Case Report**—The patient complained of burning on micturition, but no frequency or other discomfort. On examination, there was a growth about the size of a white bean protruding from the orifice of the urethra. She said that it became larger at times, and appeared inflamed, and a small amount of pinkish discharge was noted. She could not determine that there was any increase at the time of menstruation because of the vaginal flow, but the growth did seem more troublesome and larger during this cycle. Not knowing its character, I did not urge immediate surgical intervention, because it was assumed that it was an innocuous urethral caruncle. Four days after her first visit her husband stated that she was suffering intense discomfort in that region, and that he was taking her to the hospital. On examination, it was found that the growth had increased to five or six times its previous dimensions, and that a diffuse thrombosis had occurred. She was menstruating at the time. The mass was now a dark purple in color, it filled the urethra, and protruded about three-quarters of its bulk outside. Removal by cautery was done, and the biopsy revealed typical endometrial tissue, which was much distorted by interstitial hemorrhages, dilated blood vessels and thromboses. Recovery was uneventful.

The patient was 38 years of age, and, though married 16 years had never conceived. Examination of the vagina and pelvis at the time revealed nothing suggestive of pelvic endometriosis except a few hard nodules in the rectovaginal septum near the posterior vault, which, I think, undoubtedly, in view of the biopsy findings, must be looked upon as previously unrecognized endometriosis. Roentgenotherapy was instituted, and the patient did not have any further complications.

Two other cases were described in the author's monograph, "A Study of Endometriosis." In these cases the entire length of the urethra was involved but since in each case this was merely a part of a diffuse pelvic infiltration, description will be deferred.

#### SECONDARY INVOLVEMENT OF THE BLADDER WALL

The first recorded case of bladder endometriosis was that by Judd, in 1921, entitled "Adenomyoma Presenting as a Tumor of the Bladder." Two cases by Floyd Keen, reported in 1925, were entitled "Perforating Ovarian Cysts (Sampson's), with Invasion of the Bladder Wall." Then appeared Whitehouse's report, in 1926, of "Endometriosis Invading the Bladder of a Woman

who had never Menstruated” After a lapse of several years there followed a series of cases by Sauer, in 1932, Weijtlandt, in 1934, Phillips, in 1934, Perlmann, in 1934, Henriksen, in 1935, Mark, in 1937, McClelland, in 1938, and Adams, in 1938 The description of the picture varies considerably in many of these cases, as does, also, the symptomatology, but no adequate explanation was forthcoming to account for these discrepancies The symptoms vary with the type of the disease and the location of the growth Frequency and urgency usually are the first symptoms to draw attention to the bladder In over 30 per cent of the reported cases there was a previous record of pelvic operation for intraperitoneal endometriosis Usually, when the bladder involvement is a direct progression of the disease from the uterine parietes, there is no hematuria, and the bladder invasion may be felt in the anterior fornix in the region of the uterovesical contact In the invasion of the bladder by a secondary transplant from the peritoneum, the pathologic process is preponderantly in the fundus of the bladder and is responsive to the menstrual cycle Periodic hematuria, in relation to the cycle, is the *most important diagnostic sign* of the disease This sign is present in only a small percentage of cases, however, for the reasons given above In a careful review of the reported cases, the transplants of endometriosis to the bladder from an intraperitoneal endometriosis followed surgical pelvic intervention in the majority of cases Spontaneous involvement in the vesico-uterine pouch by intraperitoneal endometriosis, occurs in only about one per cent, as compared with 100 per cent of involvement in the pouch of Douglas From this, it will be seen that surgical intervention and opening of the vesico-uterine pouch in cases of intraperitoneal endometriosis, is a strong predisposing factor in the incidence of secondary bladder endometriosis

Cases of bladder involvement fall into three groups Group I—Cases of stromatous endometriosis Group II—Cases of mixed endometriosis derived from the deep layer of the endometrium by lymphatic extension through the uterine parietes Group III—Cases of involvement of the fundus of the bladder from peritoneal endometriosis

GROUP I—In this group are two cases of stromatous endometriosis which, as described in “A Study of Endometriosis,” invaded all of the pelvic structures, resembled a sarcoma, and the invasion of the bladder wall was just a part of the general involvement by contiguity In both these cases, the bladder muscularis, including its sphincteric muscle, lost its contractile function due to replacement fibrosis Incontinence ensued, followed by an acute fetid cystitis The mucosa never became appreciably involved and, consequently, there were no vesical symptoms or signs until cystitis developed The ureters were affected also, as were all the pelvic structures, and this resulted in occlusion of the ureters and destruction of the kidneys

GROUP II—In this group we find those cases of bladder involvement in which the endometriosis, made up of glands and stroma, has originated from the deep layers of the uterine mucosa and, after traversing the uterine lymphatics, invaded the bladder muscularis at the point of attachment of the

bladder to the uterus This invasion is nonresponsive to the menstrual cycle, and, when examined cystoscopically, one sees a growth, with widespread edema, and, when the submucosa is involved, there appear pearly-white cystic growths of various sizes, from millet seeds to that of a bean The growth is preponderantly in the region of the base of the bladder, frequently involving the trigone and interureteral space There is no rhythmic hematuria, but there may be microscopic blood at times

GROUP III—In this group are those cases of involvement of the bladder by transplant from a source of preexisting intraperitoneal endometriosis Thirty per cent of these cases have followed pelvic operations, and, in the majority of these, the bladder was injured surgically by separation during an hysterectomy As most of such cases are derived from intraperitoneal disease, which, in turn, is derived, in the great majority of cases, from a tubal "spill," these are responsive to the menstrual cycle, and rhythmic hematuria becomes the most efficient diagnostic sign of bladder endometriosis The cystoscopic picture varies with the time of the examination, during the interval of two menstrual periods, there is a bladder growth, surrounded by edema, congestion and blue grape-like cystic masses Hematuria is slight, but during the menstrual period the edema and congestion are very marked and hemorrhage is fairly abundant from most of the surface The growths are preponderantly in the fundus when there has not been any surgical trauma, but where the normal bladder relations may have been disturbed, the growth may invade any part of the surgically exposed bladder surface

#### SECONDARY URETERAL ENDOMETRIOSIS

Primary involvement of the ureter in endometrial disease is an exceedingly rare condition A single case is reported by Randall By primary involvement it is meant that the ureter was the primary urinary structure showing demonstrable disease It does *not* mean that the disease arose primarily in the ureter I repeat, all cases of endometriosis, according to my thesis, are of endometrial origin Randall's case is of interest It is entitled "Endometrioma of the Ureter"

Case Report—Miss C K, white, age 37, complained of right-sided pain, frequency, nocturia and hematuria She developed these symptoms in August, 1940 In November, 1940, she had a severe attack with hematuria She had gained weight recently There was no cyclical bleeding Physical examination revealed nothing abnormal except tenderness in the costovertebral angle Urinalysis was negative except for a few leukocytes, and many red blood cells

An intravenous urogram showed the left genito-urinary tract to be normal On the right there was haziness of the shadow of the kidney, pelvis, infundibula and calices The right ureter showed multiple filling defects *Clinical Diagnoses* Generalized lesion involving the pelvis, infundibula and right ureter Possible ureteritis cystica or multiple polypi of the right ureter

A cystoscopic examination showed a normal bladder After a retrograde pyelogram, the diagnosis was made of a mural growth in the distal end of the right ureter Neoplasm was to be excluded

Operation—December, 1940 Through a Gibson incision into the right retroperi-

toneal space, the ureter was freed almost to the bladder. A fusiform swelling was located about 3 cm proximal to the bladder. At this point, the ureter was found to be firmly attached to the peritoneum. The ureter was cut near the bladder and the kidney removed. Biopsy revealed typical endometrial tissue. During the operation, the peritoneal cavity was opened, and the pelvis was explored by the finger. No pelvic or abdominal pathology was encountered.

There are four cases of ureteral disease in my series. The first two cases were recorded in the Transactions of the Association of American Gynaecological, Obstetrical and Abdominal Surgeons, and last year they appeared in greater detail in the author's monograph, "A Study of Endometriosis."

These two cases were instances of stromatous endometriosis, in which the patients lived for 11 and 12 years, respectively, after the first operation, at which the disease was discovered. The two cases were so similar in all their details, that one description will cover most of the salient symptoms and pathology.

**Cases 1 and 2**—Both were women, ages 38 and 36 years, respectively. Both were operated upon for what was considered uterine fibroids. At operation, a diffuse uterine stromatous endometriosis was found. In the first patient, the disease had extended up the lymphatics of the right broad ligament into the right iliac fossa, where a diffuse growth had developed. In the second patient, the left broad ligament was invaded. Subtotal hysterectomy was performed. The reason for not undertaking a more extensive operation, was because the disease, at the time, had only been recently recognized, and there was no doubt that, clinically, we were dealing with a diffused uterine sarcoma, which had spread beyond the limits of the uterine wall, and was beyond extirpation.

The patients were treated with full doses of roentgen ray, and one of them with radium. Recurrences developed in each case and there were alternating periods of growth and recession, these corresponding to intervals during which irradiation therapy was or was not employed. Eventually, after ten years in one case, and 11 years in the other, the growth became roentgen ray-fast and no longer responded appreciably. From then on, there was a slow, relentless invasive process, which involved the walls of the rectum, bladder, vagina, and urethra. Both cases were very similar in their clinical course. The rectum and vagina became almost leaden in hardness, and the urethra became so tortuous that catheterization was impossible. Incontinence, both rectal and vesical, developed, followed by a fetid cystitis, hematuria developed, and the patients were constantly wet. This condition continued for two or more years. Eventually, nausea and vomiting supervened, and the patients sank into uremic coma. Blood chemistry showed marked retention of products of metabolism, and death followed in due course.

At autopsy, in the one case, the bladder and urethra were found to be invaded on all sides by new growth, but the mucosa was not broken through at any point. The hematuria was chiefly, if not wholly, the result of the cystitis. The ureteral walls were invaded in their lower two-thirds by the same endometriotic new growth, and though nowhere was the lumen invaded, the caliber had been impenetrably reduced by encroachment from the walls. The ureters above the constriction, were dilated and the kidneys were reduced to two small sacs with walls about one-third-inch thick. This slow degeneration of the kidneys had been progressive, evidently over years. Roentgenograms taken of the whole body while on the autopsy table, revealed no metastatic growths, but, though the lungs seemed perfectly normal, to the eye and touch, yet, microscopically, small miliary nodules were found to have permeated the pulmonary tissues—apparently, the sequela of a broken-down nodule in the internal iliac vein. Autopsy could not be obtained in the second case, but the course of the disease was parallel to the first.

Prior to her death, she began to show signs of mental aberration, followed by vomiting, and she gradually sank into an uremia coma

There were no other cases until quite recently In both of the following cases, the ureters were involved as a complication of intraperitoneal endometriosis In neither of these cases was the bladder involved, and the chief symptom was costovertebral pain on the affected side

**Case 3**—The first patient was a young woman, age 28, who had suffered for many years with pain in the right lower abdominal quadrant, which was diagnosed as appendicitis Appendicectomy was performed but the pelvis was not examined through the McBurney incision Microscopic study showed that the appendiceal mucosa was normal, but that the external surface of the organ was invaded by endometriotic growth Her condition was not improved by the appendicectomy Her pain in the right lower quadrant grew gradually worse and was now referred also to the right loin When examined by the author, a choked pelvis was found, in which the right side was more involved than the left She had been married eight years, but had never become pregnant She had severe dysmenorrhea both premenstrual and menstrual in character For several years right-sided backache was the chief symptom Six months before coming under observation, she had episodes of exacerbation of the backache, and, she thought, some fever during these periods Catheter specimen of urine revealed pus, and blood in small quantities These symptoms were not at all rhythmic and, hence, did not suggest any association with menstruation

At operation, the pelvis was a mass of endometrial blood cysts, and dense adhesions The sex organs were released with great difficulty, especially on the right side, where the subperitoneal tissues, after liberation of the ovary, showed a deep infiltration by the growth The bladder was normal to palpation, but through the extensive incision, the right ureter was found dilated above the pelvic brim, and the right kidney was reduced to a small sphere not much larger than a golf ball The left kidney was larger than normal, due to compensatory growth Three years have elapsed since the operation Her period of febrile exacerbation and urinary symptoms continued for over a year, with longer intervals of freedom and diminution of the symptoms For the past six months, she has been quite free from discomfort, and it is assumed that complete sequestration of the kidney has developed

**Case 4**—The second patient was an unmarried female, age 43, of delicate structure, fair and anemic She complained that during the past four years, she had suffered from a feeling of stiffness in her back on the left side, and, during the same period, had had repeated attacks of pain in the right lower quadrant She had had lassitude for the past four years, but this symptom became very pronounced during the last six months She stated that she had no pain on voiding, occasional frequency, and hematuria for one week about three weeks ago Her periods were regular, at 25-day intervals, lasting five days, without dysmenorrhea or leukorrhea Her urine constantly showed about 40 to 50 red blood cells (h p f), and from 10 to 25 pus cells, with occasional faint traces of albumin Every one of the 34 specimens examined showed myriads of bacteria

She was a patient of Doctor McCaffrey's and, due to her hematuria, Doctor Seng, an urologist, was called in consultation His first cystoscopic report, September 16, 1943, was as follows " Bladder mucosa normal, no tumor or foreign body seen On the trigone, there is a mild pseudomembranous trigonitis with scattered yellowish-brown cysts, about the size of a match head There are only three or four of these Right ureteral orifice identified and right ureter catheterized Specimen obtained

"The region of the left ureteral opening was edematous and, as the ureteral orifice could not be identified, the ureter was, therefore, not catheterized

"The specimen from the right kidney (about 75 cc) was cloudy Red blood cells about 25-30 (h p f)

"Roentgenograms showed the right catheter to the renal pelvis where it was looped in the pelvis, no evidence of calculus, left renal region obscured by gas Right retrograde pyelogram, with 4 cc of 12 per cent sodium iodide, showed a small pelvis of bifid type Kidney in good position Left kidney still obscured by gas

"In view of the fact that we were unable to identify the left orifice, owing to the edema about it, an intravenous urogram is indicated"

Cultures from the right kidney were negative Blood chemistry showed urea 13.2 mg per 100 cc, urea nitrogen 6.2 mg per 100 cc, uric acid 2.5 mg per 100 cc, creatinine 1.14 mg per 100 cc, and N P N 15 mg per 100 cc

September 17, 1943 Intravenous urogram At five minutes—much gas in intestines obscures both kidney regions but dye can be seen excreted in the bladder, at 15 minutes—dye can be seen in right renal pelvis, and the lower right ureter is clearly outlined—normal It is not clear whether the left kidney is excreting or not There is much gas in the region Later, no outline of left kidney visible At 30 minutes—no definite outline of left kidney *Urologic Opinion* The question of a functioning left kidney not settled A second urogram suggests a possible left hydro-ureter and left ureterocele

September 24, 1943 Cystoscopic examination under spinal anesthesia The bladder mucosa as previously reported The region of the left ureteral opening was pouting; no orifice distinguished This area was congested Attempts to pass the catheter up the ureter not successful The three small yellowish cysts in the trigone (previously reported) were congested also

*Vaginal Examination*—A large right cystic mass and a smaller one on the left, apparently without relation to the ureteral disease on that side (Doctor Seng) There was a sudden rise of temperature, with chills, after the last treatment. Symptoms and signs disappeared five to seven days later

When first seen by the author, September 22, 1943, a small asymmetrical uterus, with solid masses in both lower quadrants, was found These were more or less symmetrical and there was a possibility, among other things, that this might be a Krukenberg tumor, because the patient had suffered for a long time from gastro-intestinal symptoms Accordingly, a gastro-intestinal series was taken, with negative results Wassermann was negative

*Operation*—October 12, 1943 The upper abdomen was found to be free from adhesions There were signs of old blood, and blood pigment, about the sigmoid and coils of the small intestine The pelvis was filled with adhesions, involving both appendages, but chiefly the left, which were bound down densely to the sigmoid, mesorectum and parietal peritoneum posteriorly The left ovary contained a large "chocolate" cyst the size of a tangerine The right appendages were liberated with ease But the left with extreme difficulty During the process of liberation, the cyst ruptured and its adherent walls had to be peeled off by forceps and traction Both appendages were removed, followed by a subtotal hysterectomy The appendix, short and rigid, was also removed Exploration of the renal regions disclosed a dilated left ureter, and a kidney reduced to about one-half normal size, globular, fixed, and giving the sensation of a small thin-walled sac, filled with fluid The right kidney was about one-third larger than a normal kidney

The patient made a smooth recovery for five days, but owing to an error in orders, the house surgeon removed both the skin clips and the stay-sutures, and immediately afterwards, the patient sneezed violently, which was followed by vomiting and a severe pain in the region of the incision Inspection showed that the wound had opened in the middle third and that the intestine was protruding The tissues were clean, and the incision was immediately closed by through-and-through sutures Her recovery was smooth and uneventful



DISCUSSION —These four cases divide themselves into two distinct groups. The first two were cases of stromatous endometriosis, of a diffuse nature, arising from the stromal cells of the endometrium, and spreading to invade all the organs of the pelvis, with a slow destruction of their normal functions. Thus, we saw the rectum and bladder completely lose their muscular resilience and the development of consequent incontinence. The vagina became a rigid canal through the same cause. Infection spread up the urethra and bladder and a double pyonephrosis followed upon a slow constriction of the ureters by the new growth, with complete destruction of the kidneys, and death, owing to uremic coma. In these cases, the invasion was wholly by the lymphatics, and completely extraperitoneal. The ureteral canals were never invaded, but merely obstructed by irregular nodular invasions of the ureteral walls. In cross-section of the ureters, in places the ureteral lumen was semilunar, due to a growth on one side only. In other places the constriction was annular. The constriction in both these cases finally became bilateral, but probably not synchronously so. In the two other cases, the ureters were constricted by an endometriosis of, primarily, intraperitoneal "spill," with subsequent subperitoneal involvement of one ureter, so that destruction of the corresponding kidney became an inevitable sequela.

I have consulted Doctor Seng, and other urologists, as to the fate of these two last cases, and there is a uniformity of opinion, that one of two things will eventuate. (1) Either the affected kidney will completely atrophy and cause no subsequent trouble, or (2) a large pyonephrotic sac may develop that may require removal. The first of the two cases reported, has now gone over two years, and her general health seems to be steadily improving. The other was operated upon four months ago. Doctor McCaffery informs me that she has had kidney "flare-ups," but that these are growing less severe and less frequent. It will be noted that in neither of these two cases was the ureteral disease complicated by endometriosis of the bladder.

An effort has been made in the literature to classify bladder endometriosis as primary or secondary. This subdivision I cannot endorse, because I have tried to demonstrate that all cases of endometriosis of whatever type, or in whatever pelvic site, are endometrial in origin. Henriksen states that his case of vesico-uterine endometriosis was of primary vesical origin. He states "I feel that the term 'primary vesical endometriosis,' should be limited to those cases in which no demonstrable contiguity with uterus, fallopian tubes or ovaries is present, and in which there has been no surgical trauma of the bladder wall or its peritoneal reflection." That is not a very convincing argument. One might as well contend then, that all tumor metastases in the liver are primary because there is no continuity with the primary growth. By the same token, Krukenberg tumor of the ovaries would be primary ovarian cancer, and many other examples could be added to prove the falsity of such a contention.

Ernest Mark's statements *apropos* to this subject, are of significant interest. "The case reported by Whitehouse received no surgery. There was

no involvement of the mucosa This case, like that of Henriksen, did not have cystoscopy prior to operation, and the endometriosis arose from tubal and ovarian involvement in the ectopic process and involved all the serous and muscular coats of the bladder It is my opinion that this case, and others of like character, should not be included under the heading of bladder endometriosis and, most certainly, cannot be termed endometrioma of the bladder" May I add, parenthetically, that the term "bladder" in these cases, as outlined in my study, should be used in such cases merely as a regional denomination, and not in a sense of primary origin of the disease

In my series, the first two cases were ones of stromatous endometriosis, in which the ureters were involved late in the disease—to be more specific, ten, or more, years after the disease was discovered The ureters were just part of a general invasive disease involving all the pelvic structures, with eventual destruction of the kidneys, and death owing to uremic coma In these cases, the bladder, though extensively involved as to its musculature, maintained its retentive power until the sphincter became involved, and incontinence developed, following this, acute fetid cystitis developed, and ultimately double pyelitis followed In the two other cases the disease was not parametrial from the uterine parietes as in the former two, but was of the "spill" character, through the fallopian tubes, and the ureter in each case became involved in its pelvic course, by transperitoneal invasion The bladder was not involved in either case, except by local edema at the corresponding ureteral orifice, due to lymphatic block

In these two cases, the outstanding symptoms were, therefore, not vesical in origin, but resulted from the diseased kidney, and frequency and urgency were conspicuous by their absence before urologic intervention

These two cases, I think, are the first to be reported of transperitoneal ureteral stricture without previous involvement of some layer of the bladder In the cases of involvement of the bladder mucosa, the triad of symptoms—frequency, dysuria, and hematuria—are fairly constant In only a small percentage of cases, can the hematuria be shown to synchronize with the menstrual cycle When this is present, the diagnosis is much facilitated

*Symptoms*—From what has gone before, it is quite evident that the symptoms of endometriosis depend upon several factors (1) The part of the urinary tract affected, (2) the type, and, therefore, the origin of the endometriotic transplant

The case of urethral endometriosis was indistinguishable, on inspection, from an ordinary urethral polypus

In bladder endometriosis, it is commonly asserted that the three fairly constant symptoms are frequency, urgency and hematuria Hematuria is frequently only microscopic in cases where the new growth is chiefly muscular, and the mucosa merely shows signs of lymphatic and vascular obstruction In cases of transperitoneal involvement of the bladder mucosa, the bladder disease is usually responsive to the menstrual rhythm and the hemorrhages are, therefore, accentuated rhythmically

Visually, through the cystoscope, there is usually a tumor, with marked edema, and in the nonresponsive cases the cysts, if visible, are of a pearly opalescence, but in the responsive type, the cysts are of a dark blue grape-like color, with fairly profuse hemorrhage from these during menstruation. In the two reported cases of stromatous endometriosis of the bladder, the chief symptoms arose out of lack of contractility of the bladder and sphincter musculature, followed by incontinence and cystitis. In the two cases of ureteral obstruction there were no outstanding vesical symptoms, but severe costo-vertebral pain forced these patients to seek relief. In these cases, there was destruction of the kidney on the side of the obstructed ureter. The other kidney had hypertrophied compensatorily. In the two cases, where both ureters were blocked, the patients died of uremic coma, consequent upon the destruction of both kidneys.

*Treatment*—The treatment resolves itself into the same as that for endometriosis elsewhere in the pelvis. I cannot see the rationale, or the efficacy, of excision of the bladder tumor when the agency which brought about the bladder involvement is still left in operation.

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# AN APPLICATION OF STAGING IN THE REMOVAL OF DIFFICULT WILMS' TUMORS

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IT IS NOW WELL RECOGNIZED that there exists a group of renal neoplasms of mixed cellular components which, although they may occur from fetal life up to late adult life, are most frequently found in infancy and early childhood, where they make up approximately one-fourth of all tumors seen. They are characterized by rapid growth to bulky size, metastasize particularly to the liver and lungs, and have a quickly fatal termination. The relative absence rather than the presence of symptoms is striking in view of the marked physical findings. The earliest report of such an entity was written by Gairdner,<sup>6</sup> who, in 1828, described a case of "fungus haematodes of the kidneys." The clinical setting and postmortem findings in his patient were typical, although bilateral involvement was present. Eberth<sup>4</sup> in 1872, was the first to present a microscopic description of the process. In 1894, Birch-Hirschfeld<sup>3</sup> first used the term embryonal adenosarcoma, since designated by Ewing<sup>5</sup> as embryonal adenomyosarcoma. Wilms,<sup>16</sup> in 1899, thoroughly reviewed and clarified the subject in a monograph titled "Mixed Tumors of the Kidney," and the eponym "Wilms' tumor" is now generally accepted. The term renal embryoma, although less specific in its connotation, has, also, through frequent usage come to be identified with these neoplasms.

The proper method of treating Wilms' tumors has been the subject of a good deal of discussion. The usually marked, and occasionally phenomenal, regression in size produced by external irradiation has led to widespread use of this form of therapy. That fully viable-appearing tumor remains after heavy dosage has been shown by Bothe,<sup>1</sup> and is reflected in the uniformly poor results following the use of roentgenotherapy, either when used alone or as a preoperative adjunct.

The results following surgery alone, however, as reported by Mixter,<sup>14</sup> and Ladd and White,<sup>9</sup> have, by comparison, been so far superior to those, that one must accept that primary nephrectomy undertaken without delay is unequivocally the best method of treatment at the present time and should be promptly carried out whenever possible. There seems little doubt but that their results were due to two main factors: the saving of very valuable time in dealing with an acute neoplasm by omitting preoperative roentgenotherapy, and the employment of a transperitoneal approach. Much stress has been placed by Ladd on the primary ligation of the renal pedicle before the major portion of the tumor is disturbed, in order to prevent the possible dissemination of tumor emboli incident to manipulation. Recently, McDonald and Priestley<sup>12</sup> have demonstrated renal vein involvement in 45 per cent of

31 Wilms' tumors studied, so that initial pedicle ligation would appear to be of more than theoretic importance

A second important advantage of the abdominal approach, heretofore not mentioned but certainly just as important as the care of the hilus, is the ability provided for excising the kidney in its anatomic envelope—Gerota's fascia. The renal capsule is normally not a very substantial covering (Fig 1) and, as a result of the stretching produced by the tumor, it may become extremely thin (Fig 2). Surrounding the capsule is the perinephric fat, which is usually diminished in amount or absent around the embryomas. Surrounding this, in turn, and completely enveloping the kidney is the renal fascia, first described by Gerota,<sup>7</sup> in 1895.

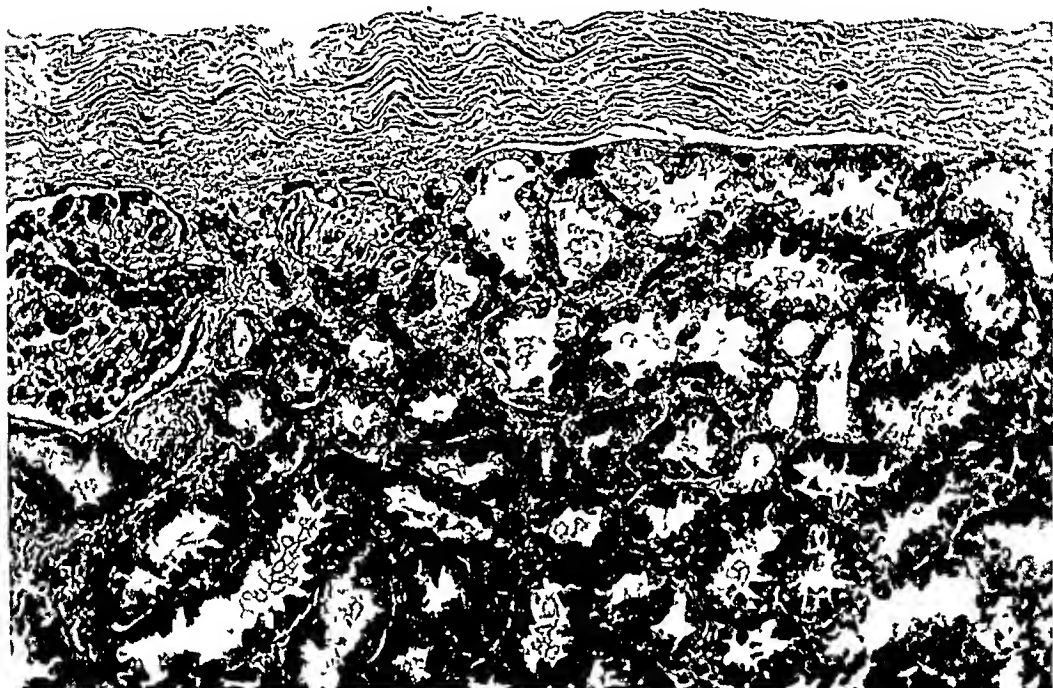


FIG 1—Normal kidney with capsule attached, to indicate its thickness relative to underlying structures

Gerota's fascia, synonymously referred to as Gerota's capsule, renal fascia, perirenal fascia, fascia propria, and tunica fibrosa, arises from the transversalis fascia as a short band which splits into two layers to invest the kidney and the perirenal fat in a fairly thick posterior layer (fascia of Zuckerkandl), and a somewhat thinner anterior layer (fascia of Toldt). By some anatomists (Davies,<sup>2</sup> and others) these are looked upon as concentrations of a more peripheral portion of the sub- or extraperitoneal fascia. There is general agreement, among those who have so carefully worked out the anatomy of this capsule, that the posterior layer attaches to the bodies of the vertebrae in front of the psoas muscle. The precise disposition of the anterior layer has been the subject of some dispute. Gerota originally described it as crossing the midline anterior to the renal and neighboring great vessels and continuing as the corresponding layer of the opposite side. Southam<sup>15</sup> was able to trace

## WILMS' TUMOR

FIG. 2

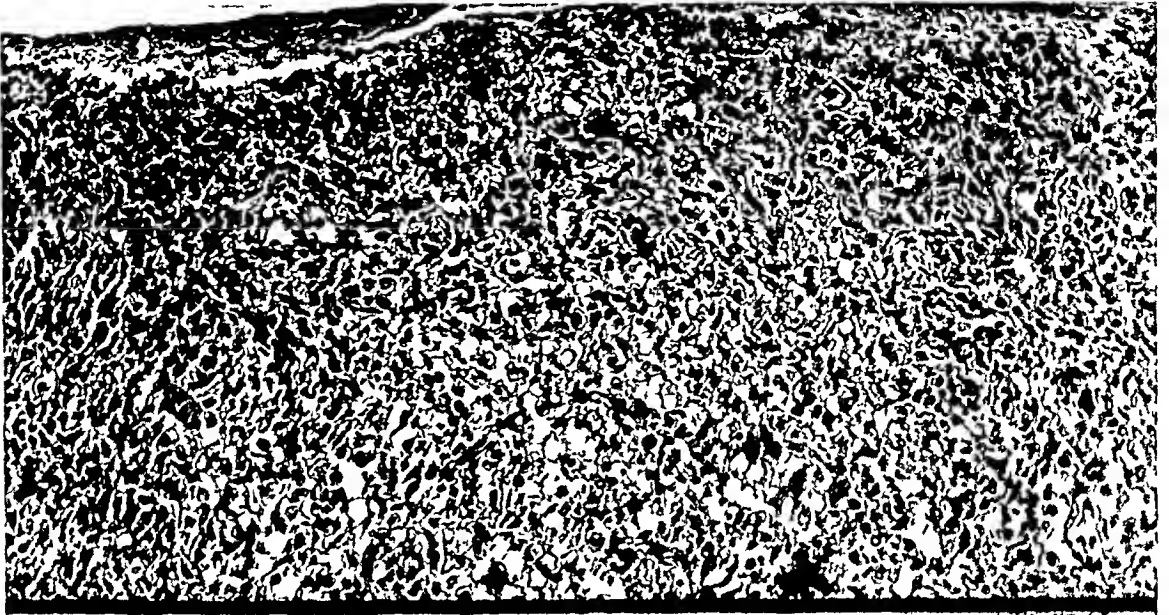


FIG. 3

FIG. 2—Marked thinning out of capsule over bulky Wilms' tumor. In many areas (not shown) capsule is only one cell thick. (Section from case presented.)

FIG. 3—From another case of Wilms' tumor, indicating infiltration of renal capsule and renal fascia by tumor cells. As anticipated, recurrence in the tumor bed developed shortly following nephrectomy.

the fascia anteriorly only as far as the pancreas and the root of the mesentery. Considerable support was added to Southam's work by Mitchell<sup>18</sup> who, after injecting an emulsion of barium into the perinephric space, took radiographs and noted strict localization of the barium to the side injected. Spread across the midline occurred only after a considerable amount of the material had been injected and, then, at the level of the lower lumbar vertebrae. Quite recently, the problem has been clarified by Martin,<sup>11</sup> who traced the anterior layer across the midline from one side to the other, but found that both the anterior and posterior layers split on the medial aspect of the kidney to completely surround it and there are pierced by the hilar vessels (Fig 4).

At the upper pole of the kidney both the anterior and posterior layer of fascia fuse with that on the undersurface of the diaphragm. At the lower pole

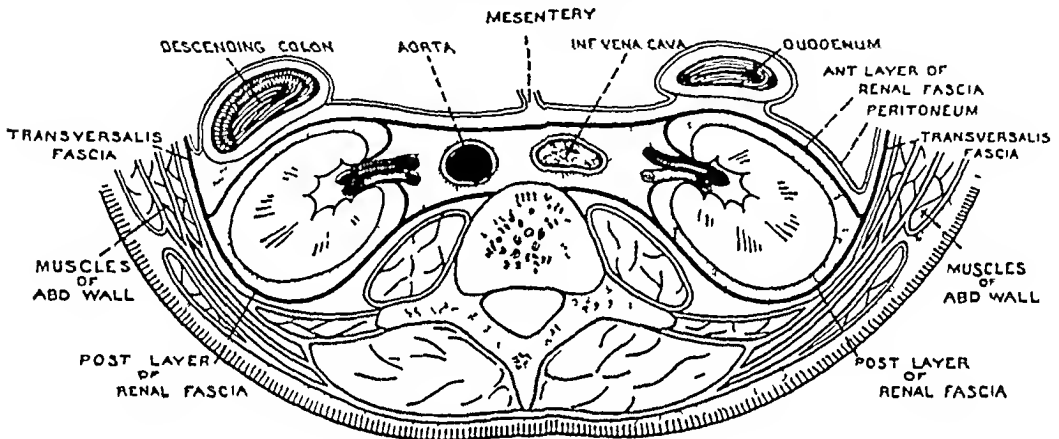


FIG 4—Transverse section showing arrangement of renal fascia (From Cunningham's Anatomy, 8th Edit, pp 1464)

of the kidney they do not blend, but invest the ureter and gradually fade out as they are traced downward (Fig 5).

Surrounding the perirenal fascia posteriorly, lying chiefly between it and the parietal musculature, is the paranephric fat often referred to as the fatty capsule of the kidney. This is present in lesser amount anteriorly between the same fascia and overlying viscera and is a derivative of the subperitoneal fascia. This latter structure in its typical fibro-areolar form covers the kidney only where the kidney lies immediately beneath the peritoneum.

In removing the renal fascia with the kidney, therefore, the fascia must be divided above, below, and mesial to that organ. Its incision mesially is necessary in order to approach the hilar vessels. The removal of Gerota's fascia through a lumbar approach would be difficult, and it is doubtful whether it could ever be done neatly or in its entirety under any but exceptional conditions. Usually, in lumbar nephrectomies, this fascia is entered posterolateral to the kidney from which it is completely stripped in order to secure the hilar structures. With most embryomas, such a procedure would be almost certain to result in future recurrence.

The operability in Wilms' tumors, as with most tumors, will depend largely on the skill and experience of the surgeon. Mixer,<sup>14</sup> in 30 cases,



reported an operability of 73 per cent. Apart from metastases, the factors responsible for the operative rejection of most cases have been local. This is emphasized by the numerous statements in the literature advocating pre-operative roentgenotherapy as a means of diminishing the size of the tumor and, thereby, facilitating surgery. Since the difference in end-results between

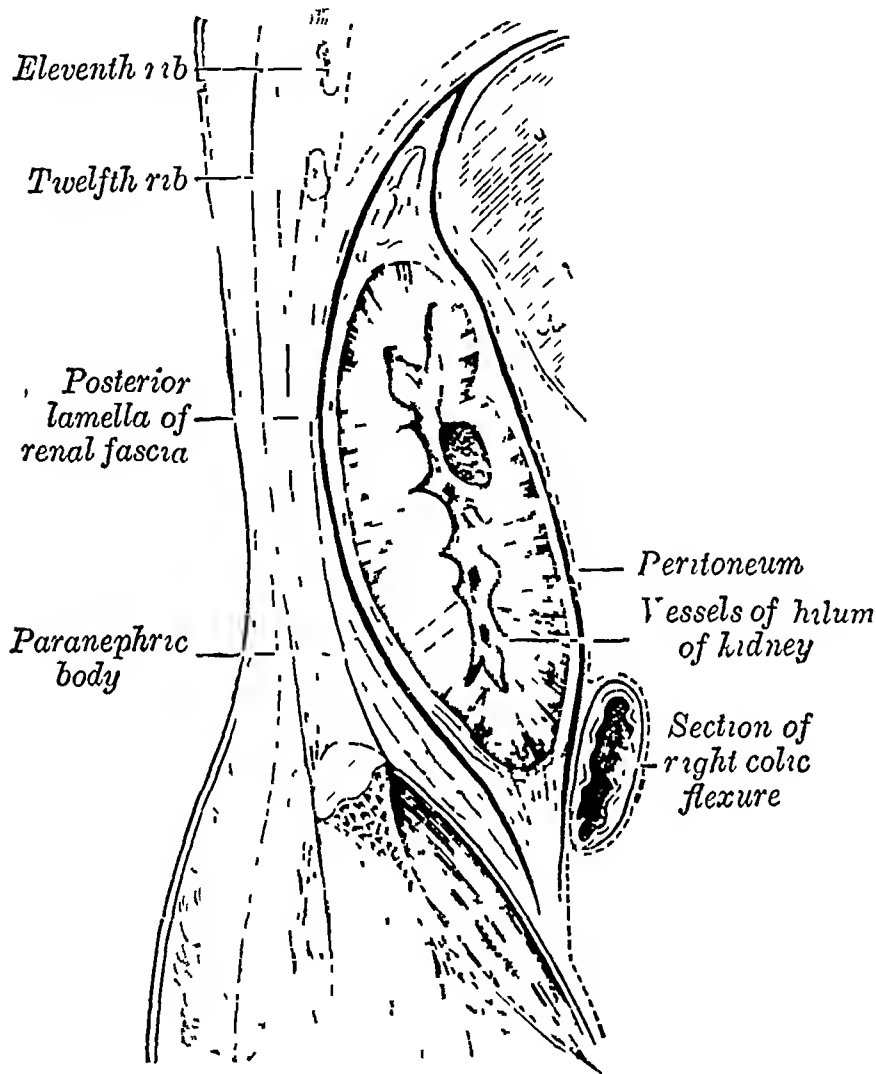


FIG 5.—Disposition of renal capsule as seen in sagittal section through the posterior abdominal wall (From Gray's Anatomy, 22nd Edit pp 1212)

the preoperatively irradiated and the primarily operated patients now points to the danger of the first mentioned course, there appears to be excellent reason for attempting to extend the operability by dividing the operative procedure up into stages, if necessary, in order to carry out the prompt removal of the tumor with minimum risk. There are two main technical difficulties involved: first, the handling of the pedicle and, second, the control of the bleeding in freeing the kidney. In bulky tumors, considerable distortion of the normal anatomy takes place. The colon, duodenum, pancreas, spleen, etc., are usually considerably displaced, along with their blood supply. Usually, the mass completely overlies its pedicle, making approach to the vessels difficult. This, added to the possibility of marked shortening of the renal veins or adherence of the mass to, or actual invasion of, the wall of the vena cava,



may convert what was intended to be the preliminary to a nephrectomy into a time-consuming, hazardous procedure in itself. Another difficulty frequently encountered is vigorous bleeding from the markedly dilated and thinned-out perinephric veins. The danger, here, arises less from blood loss than from interference with exposure and the dependent uncertainty of dissection.

A case presenting these difficulties is, herewith, described, and demonstrates a workable method of staging. It is probable that several variations of such a procedure are possible, but the anatomy of the kidney as well as the natural tendencies of Wilms' tumors, suggest that the procedure here followed will be found to be the one most frequently useful.

#### CASE SUMMARY

**Case Report**—Hosp No 3719 C A, a 12-year-old boy, was admitted to the hospital, January 16, 1942. His parents stated that in October, 1941, after an appendectomy, an abdominal mass had been noticed which had been increasing rapidly in size. Intermittent hematuria had been present, and back pain had been prominent. According to the referring physician, no mass had been found at previous celiotomy.

Examination showed a bulky, rubbery mass extending from beneath the right costal margin to the symphysis pubis. It occupied the entire right abdomen and extended beyond the midline to fill almost half of the left abdomen from the umbilicus laterally.

Urinalysis was negative, no red cells were present. Blood examination revealed an hemoglobin of 10 Gm per cent (70 per cent), and R B C of 3.9 million, and a W B C of 11,550, with 78 per cent granulocytes. The N P N was 18.6 mg per cent.

A roentgenogram of the chest showed no metastases, and an intravenous pyelogram indicated a nonfunctioning right kidney.

**First-Stage Operation**—January 23, 1942. The abdomen was entered through a large right-sided T-shaped incision. The tumor had displaced the liver anteriorly. The right colon lay in the left side of the abdomen. The stretched parietal peritoneum, lateral to the ascending colon, was incised and bluntly stripped off the left side of the mass in an attempt to approach the renal pedicle. No right lateral mobility could be obtained, however, because of marked adherence of the left renal vein to the posterior aspect of the tumor. Only a single left renal vein could be identified, but it was nevertheless divided. The vena cava could then be seen lying in a groove on the midposterior aspect of the mass with which it communicated in two places. The communications represented the original right renal veins, two in number, which as a result of the expansion of the tumor had become so shortened and broadened that no pedicle any longer remained and a direct entry of blood from tumor into the vena cava had been established. Each of these flattened structures measured about 5 cm in breadth, the upper one also encompassing the left renal vein orifice in its scope. With the vena cava controlled by circular tapes above and below the mass, a longitudinal segment of the wall of the vena cava, corresponding to the entry of the upper of these two veins, was removed and the lumen closed using a continuous interlocking suture of fine silk. The right renal artery supplying the mass was next divided. At this point, the patient appeared to be having considerable respiratory embarrassment and it was reported that the blood pressure had been slowly but steadily dropping despite continuous blood replacement. A great deal remained to be done but it was feared that any prolonged hypotension might too seriously interfere with the function of the right kidney. The procedure was terminated, therefore, with the expectation of completing the removal at a later time.

Postoperatively, the child did very well. Repeated examinations of the left testicle

failed to demonstrate any swelling and the daily N P N never rose higher than 28.3 mg per cent

*Second-Stage Operation*—January 29, 1942 (six days later) The abdomen was reopened, and in less than ten minutes dissection was being continued from the point which it had taken three and one-half hours to reach in the first stage. Moreover, the capsular veins which had been tremendously dilated and thin-walled at the first stage now were thrombosed, making dissection not only easier but much more precise.

Tapes were again placed around the vena cava and the lower venous connection between it and the tumor was severed by removing a similar longitudinal segment from



FIG 6—Cut surface of tumor in case presented. Shows numerous cystic spaces and thinned out zone of normal kidney ( $2/3$  actual size)

the vena cava. This second opening was closed in an identical manner as was the first one. The tumor appeared to be quite adherent to the diaphragm, and in carrying out sharp dissection the tumor was entered, with resulting spillage. The area of adherent diaphragm was extrapleurally excised. Sharp drops in blood pressure occurred during these manipulations. The parietal peritoneum was resutured, a flank drain was placed, and the abdomen closed.

The tumor weighed 1,760 Gm (Fig 6). It had a fairly dense connective tissue capsule in most places, but in some areas this was extremely thin. On microscopic examination, the typical appearance of Wilms' tumor was present. There was no vein involvement observed.

The postoperative course was uneventful. Between February 12 and March 6, 1942, 2,000 roentgens (measured in air) was given to each of two 15- x 20-cm fields, one anterior and one posterior. Other factors were 200 KV, 15 ma, 50 cm T S D,

and 1 mm cu and 1 mm al filter This produced some erythema of the skin, but no moist reaction

Follow-up has now continued more than two years, and the child has remained well, and is developing normally

COMMENT—Although some form of a rectus incision may be employed satisfactorily in removing smaller tumors, a large T-shaped incision would seem to be more useful in the removal of the larger ones The horizontal limb must often extend from costal margin to pubis, with a vertical limb extending laterally at the level of the umbilicus well into the flank The advantage of this lies in enabling the surgeon to roll the tumor laterally with a minimum of squeezing to gain access to the pedicle

Often the colon and, to a lesser extent, the more medially situated structures are displaced anteriorly and medially by the expansion of the mass This often leaves a wide stretch of peritoneum between the lateral border of the colon and the abdominal wall This peritoneum and its own underlying fascia are unnecessary for subsequent closure and may, therefore, be left on the tumor Moreover, since the anterior layer of the renal fascia is thinner than the posterior layer, the removal with the kidney of the peritoneum and subperitoneal fascia presents an added safeguard against tumor recurrence

Complications, such as tumor adherence to, or definite invasion by tumor of, segments of the inferior vena cava, the projection of large thrombi from the renal vein into it, or the conversion of the renal veins into renal sinusoids by distortion and shortening incident to tumor growth (as occurred in this case) are more apt to occur on the right than on the left side because of the shorter length of the right renal vein (or veins)

Small to moderate defects left in the vena cava by longitudinally excising portions of its wall may be closed by suturing with a continuous over-and-over or interlocking black silk suture In repairing after large excisions the lumen may occasionally become so narrowed as to partially obstruct the return flow of blood When this occurs, so much bleeding may result at the suture line that ligating the vena cava may become necessary This happened recently in a case of carcinoma of the kidney It is now well known that ligation above the entry of the left renal vein is almost invariably fatal but that ligation below that vessel is usually followed by the development of a good collateral circulation<sup>17</sup> Since the necessity for this procedure usually occurs during surgery on the right kidney, the location and identity of the left renal vein must be positively established before any ligating of the vena cava is done

It is interesting to note that in the case presented here, a right nephrectomy and a ligation of the left renal vein were simultaneously accomplished without subsequent untoward results Multiple renal veins on either side are common, but both at the time of ligation and at the second stage of the procedure, attempts to find another left renal vein in this case were unsuccessful It must, therefore, be assumed that sufficient collateral circulation of the left kidney was immediately established to maintain a normal N P N post-operatively The collateral renal venous return may take place by way of

the left spermatic, renal capsular and the adrenal and azygos systems. The renal capsular vessels have established communications with the phrenic, portal, ureteral, and spermatic veins. Lejars<sup>8, 10</sup> was able to demonstrate renal-azygos communication in 80 per cent of cadavers he examined. It is easy to appreciate that the situation here is in no way analogous to ligating the inferior vena cava above the left kidney since the factor of caval back pressure is absent in the case presented.

Occasionally, very marked tortuous dilatation of the capsular veins is seen in kidney tumors. After the hilar vessels have been ligated and several days are permitted to elapse, these vessels are either considerably diminished in caliber or have become thrombosed. Dissection of the tumor capsule may then be carried out accurately without the handicap of profuse bleeding which may intermittently obscure the field.

In several recent cases, capsular vein engorgement was associated with extensive invasion of the renal veins by tumor. In one of these a single right renal vein was completely occluded by a sausage-like tumor thrombus. It is possible that the surgeon may be able to predict major involvement of the kidney veins at the operating table with considerable accuracy.

Over 90 per cent of the surgically-treated Wilms' tumors that are not cured will recur or metastasize during the first year following operation. It is extremely rare for the disease to reappear after the second year. The case presented has now gone two and one-half years since operation, and therefore, may be reasonably expected to remain well.

#### SUMMARY

1. The proper treatment of Wilms' tumors is discussed. The results indicate that preoperative roentgenotherapy does considerable harm by delaying nephrectomy. Local postoperative irradiation should probably be administered following specific indication (not empirically) and a more careful attempt made at evaluating its results.

2. In view of the high incidence of local recurrence following the removal of renal embryomas, more attention should be paid to the advantages to be derived from a clearer idea of Gerota's fascia.

3. It seems likely that if preoperative roentgenotherapy is to be discarded as an aid to surgery, and if a high operability and low mortality are to be maintained, certain cases will have to be staged.

4. Such a case is presented because it demonstrates so well the difficulties which may be encountered and what may be accomplished to overcome them.

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## ANNALS OF SURGERY

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# EXTERNAL PIN TRANSFIXION OF FRACTURES

## AN ANALYSIS OF EIGHTY CASES

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THE INTEREST MANIFESTED in the use of external pin fixation has prompted us to report the results of our experiences with 80 cases treated during the past three and one-half years on the New York University Division of Bellevue Hospital

Roger Anderson, Haynes, Stader and many other advocates of external mechanical pin fixation of fractures have endeavored to facilitate the management of fractures by painstaking inventions and creations of refinements in their instruments and technic

At first glance, one is overwhelmed by the ingenious contrivances, which seem so mechanically intriguing. One becomes further impressed when the patient is ambulatory and demonstrates some mobility of his joints

However, in our experience, the high incidence of discharge around the pin sites alone, would be sufficient reason to preclude the use of the method as a routine procedure (Table I). Nevertheless, this method of treatment

TABLE I  
INCIDENCE OF DISCHARGE FROM THE PIN SITES

	Discharge from Pin Sites		Osteomyelitis Pin Site		Sepsis	Died
	No of Cases	Per Cent	No of Cases	Per Cent		
Humerus						
Simple	4	5%	3	75%	No	
Compound	1	1%			No	
Ulna						
Infected	1	1%	1	100%	1	100%
Tibia and fibula						
Simple	31	38%	10	32%	10	32%
Compound	23	28%	6	26%	4	17%
					1*	1*
Neck of femur	7	8%	7	100%		
					5	5
Femur						
Simple	12	15%	9	75%	3	33 3%
Compound	1	1%	1	100%		
					1†	1†
					1‡	1‡
Total	80	100%	37	46%	18	22 5%
					8	8

\* Died on 75th day of cerebral thrombosis pneumonia cirrhosis of liver and sepsis

† Died on 2nd day, 103 years old—Russell traction for 19 days, restless and unmanageable, then pin fixation

‡ Died on 36th day from multiple injuries

should not be entirely discredited. Many of the infections around the pin sites may have been averted by laying less stress on ambulation and mobilization of joints, by immediately immobilizing the extremity and pins in plaster and by applying a new encasement when the swelling subsided. Our high

mortality in hip fractures may have been prevented by employing internal instead of external pin fixation. We have not been able to obtain the excellent results which the proponents claim for the "castless" external pin fixation for fractures of the hip. In our opinion it should not be used for fractures of the hip.

Nevertheless, external mechanical pin fixation with plaster is useful if restricted to certain problem fractures in which conservative treatment will not give a satisfactory clinical result.

While it is not the purpose of this paper to analyze and discuss the various forms of mechanical pin fixation and the principles and methods of the procedures employed, we cannot refrain from calling attention to some of the fundamental principles evolved as a result of the use of the methods by the proponents and by our own experience.

#### 1—PRINCIPLES IN THE APPLICATION OF EXTERNAL PIN FIXATION

- 1 Meticulous surgical technic
- 2 Knowledge of basic anatomic and mechanical factors in reposition of fragments
- 3 Simultaneous skeletal traction, countertraction, rigidity of the pins and of the fragments
- 4 The pins should be rigid and large and have no elasticity or spring
- 5 Sustained impaction or contact
- 6 Avoidance of sustained distraction
- 7 Avoidance of encroachment of the pins on (1) major neurovascular structures, (2) capsule, and (3) articular surfaces
- 8 Use of two or more pins in each major fragment if feasible, one pin in a fragment does not prevent shearing, rotation or redisplacement
- 9 (a) Half pins should penetrate the opposite cortex to assure stability and firm leverage
- (b) The points of the half pins should not project beyond the opposite cortex into muscles, and cause irritation and inflammation
- (c) Half pins should preferably be inserted on the medial side of the tibial fragments where the bone is devoid of muscles
- 10 (a) When using half pins converging angular insertion of the pins to the transverse and longitudinal diameter of the fragment, engages a larger cross-section of bone and assures better control during manipulation of the transfixion connecting rods and for immobilization
- (b) To facilitate traction other than by the use of an anatomical splint, the distal through-and-through pin, inserted at right angles to the long axis of the shaft at the site of election, permits utilization of the distal pin for more effective direct traction
- (c) "The Haynes self-tapping pin is a combination drill, tap and pin in one unit. The drill is the proper size for the root diameter of the tap which enables the tap to cut a clean thread in the cortex and

# PIN TRANSFIXION OF FRACT





in continuing to turn the pin you have a full thread in the cortex with the drill point anchored in the opposite cortex. The thread is intended to prevent the pin from coming out and should not create pressure to cause necrosis. The Haynes pins are inserted at right angles (1) because it is easier to insert, (2) the pressure line is the center of the bone and it would be more rigid than if inserted at an angle, and (3) the greater the angle the greater the load the pin has to carry."

- 11 (a) *Plaster of paris incorporating the pins and adjacent joints is indispensable in the use of external pin fixation in simple fractures of the tibia and fibula, and in some simple fractures of the femur. It is absolutely imperative for compound fractures.*
- (b) With evidence of diminished swelling and movement in plaster, the connecting rods should be refastened and a new encasement applied to prevent friction of the soft tissues against the pins and to more rigidly immobilize the fragments.

12 If there is no loss of bony structure and *plaster is employed*, the pins should be *extracted within three to five weeks in tibial fractures and within five to seven weeks in femur fractures*. Before extracting the pins determine if the encasement fits snugly, if not, fix the pins and the connecting rods, change the anterior or posterior shell or the entire encasement and check roentgenographically.

*Joints—Comminuted Fractures*—External transfixion with strong Kirschner wires by closed or open reduction and immobilization of the transfixion pins and adjacent joints in skin snug-fitting plaster encasement is desirable where distal skeletal traction is not feasible or fails to realign comminuted fragments. This procedure is particularly applicable to extensive comminuted simple and compound fractures of the elbow. The Van Gorder incision for exposure of the articular surfaces is especially desirable as the fragments can be visually fitted on to the Kirschner wires which are inserted through the intact skin over either condyle. A plaster jacket, with an anterior and posterior moulded plaster of paris splints, with circular turns, is applied to the arm with pyramids of plaster fixing the protruding wires. The pins are extracted in four to six weeks (Fig 1—a, b, c, d and e).

In simple or compound comminuted fractures of the astragalus, a similar procedure is advocated. The anterior or posterior shell of plaster should be changed alternately when the swelling subsides.

## 11 — PROCEDURE OF REDUCTION FOR SIMPLE AND COMPOUND FRACTURES

Where a Roger Anderson reduction splint is available, the use of the self-aligning splint will greatly facilitate reduction. The anatomical splint, or chassis, is not absolutely necessary to effect reduction (Fig 2). Traction, manipulation and reduction can be obtained on an ordinary traction table. This is facilitated by inserting the basic traction pin in the most suitable site for the most effective traction.

## PIN TRANSFIXION OF FRACTURES

*Fractures of the Femur* —A strong Steinman nail is inserted just above the adductor tubercle. The desired number of pins are then inserted at the sites of election (Figs 3—a, b, 4—a, b, and 5—a, b). Slight traction is exerted through the distal pin and fixed to the traction table with the knee flexed as much as the location of the fracture would demand. Rotation is corrected by manipulating the pin rods and, almost simultaneously, the extra



FIG 1d Encasement removed, site of skin graft. Pin extraction June 30, 1942  
FIG 1e January 6, 1944—range of mobility 60°–80°

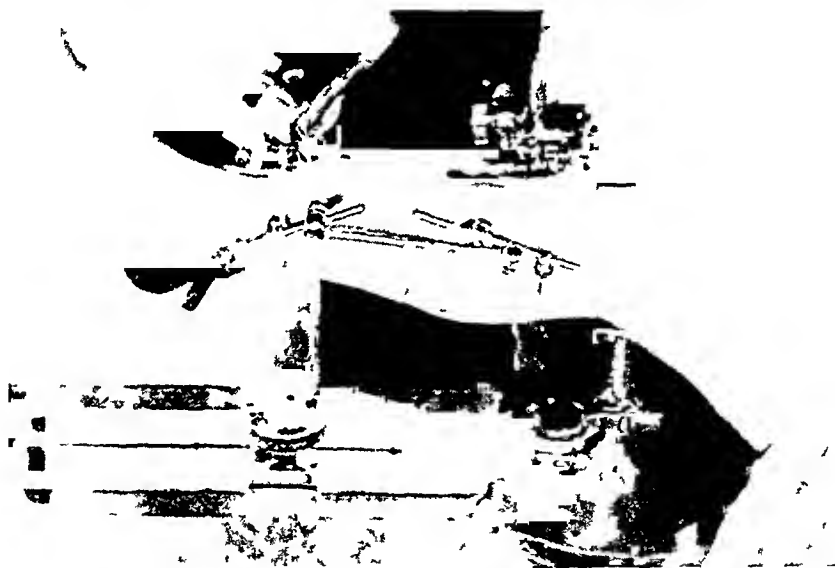


FIG 2 —Roger Anderson reduction splint used for a fracture of the tibia and fibula, through and through pins, fracture units joined with connecting rods. Plaster slabs around pin sites

traction is applied in the direction of the long axis of the fragments. After the fragments are manipulated into position, the rods connecting the dual, triple or quadruple pins are clamped to the long connecting fixation rod, or rods, to maintain the fragments in position. After verifying the corrected position of the fragments roentgenologically a double plaster spica is applied which also incorporates the pins.

*Fractures of the Tibia and Fibula* —A Boehler Braun splint, a Boehler traction frame, a traction or an ordinary operating table may be used. The

Boehler traction frame or traction table is especially desirable if the fracture is compound as the wound is more readily accessible for débridement. Traction may be effected through the os calcis if the fracture is in close proximity to the ankle. More effective traction and reduction is facilitated if the distal pin can be inserted through the tibia, preferably two finger's breadth above the internal malleolus. The desired pins are then inserted into the fragments (Fig 6). The short connecting rods are attached to their pins

FIG 3a

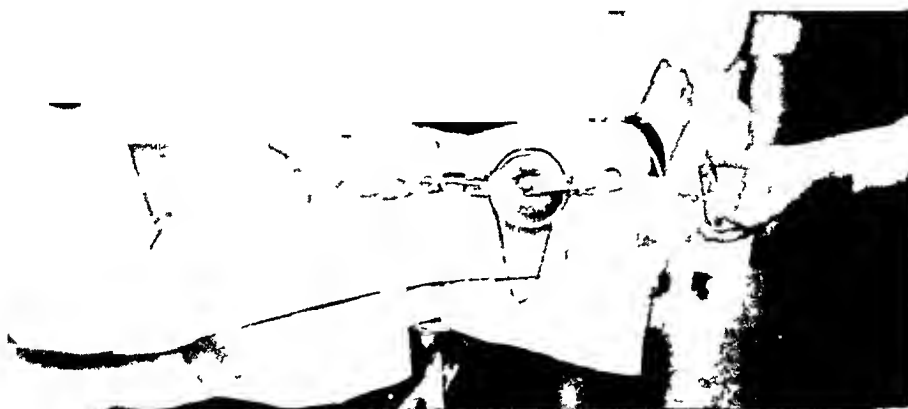


FIG 3b

FIG 3 —a On ordinary operating table, lines indicating desired sites of insertion of half pins  
b Half pins inserted, intermediate connecting rod connected to fracture units

and the fragments are manipulated into position. The two units of dual, triple or quadruple pins and their connecting rods are fixed to each other by one or more connecting rods. A moulded anterior, posterior and circular plaster encasement incorporating the pins is applied from the toes to the groin with the knee in 30° flexion.

*Humeral Fractures*—The two half pins in the proximal fragment are inserted slightly anteriorly and laterally so as to converge obliquely backward. The two half pins in the distal fragment are inserted posteriorly so as to converge obliquely forward. The short connecting rods are attached to their pins. The right-angled flexed elbow and the midpronated forearm is then fixed on a traction table with bandages over felt. Or a Kirschner wire may be inserted one inch below the olecranon process and fixed to the adjustable

## PIN TRANSFIXION OF FRACTURES

traction arm. The fragments are then manipulated into position. The long connecting rod is clamped to the fracture units. A plaster spica is then applied.

*Forearm Fractures*—Depending on the location and the direction of the displacement of the proximal fragments, the flexed forearm is placed in a

FIG 4a

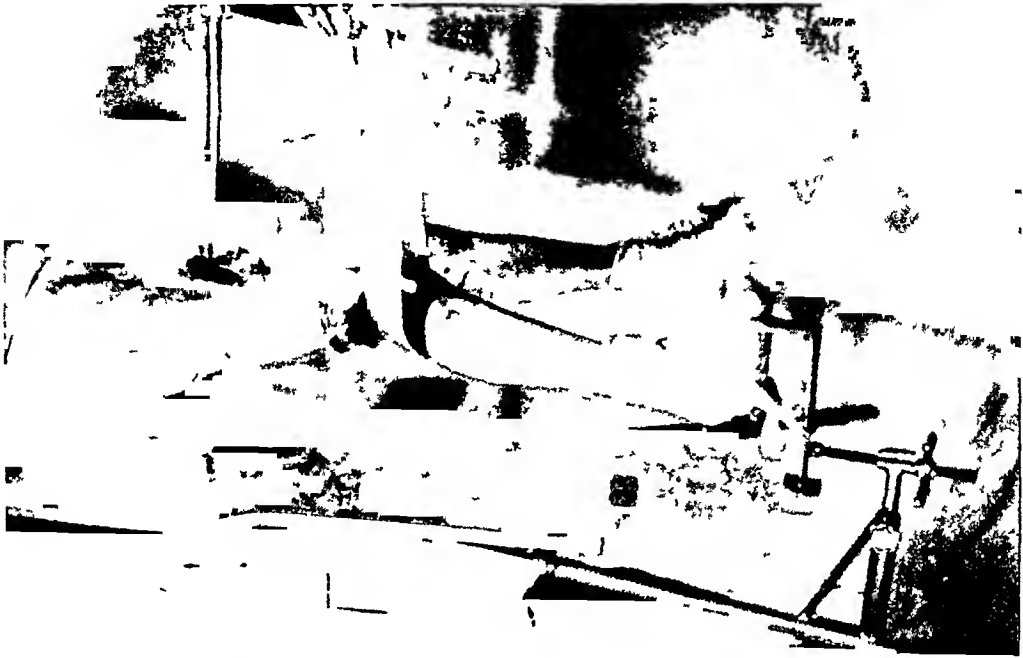


FIG 4b

FIG 4 —a Hawley table—through and through and half pins inserted  
b Plaster spica incorporating projecting pins

position of supination, midpronation, or complete pronation. A pin is then inserted through the radius and ulna, two finger's breadth above the tip of the styloid process. Where the fracture is in close proximity to the wrist, the hand is placed in complete pronation with the four fingers in extreme

adduction. A Kirschner wire is then inserted through the second metacarpal bone at the base of the web between the thumb and index finger. The pin should penetrate at least two metacarpal bones. The pin is connected to a caliper and a rope which extends over a pulley on the traction ex-

FIG 5a

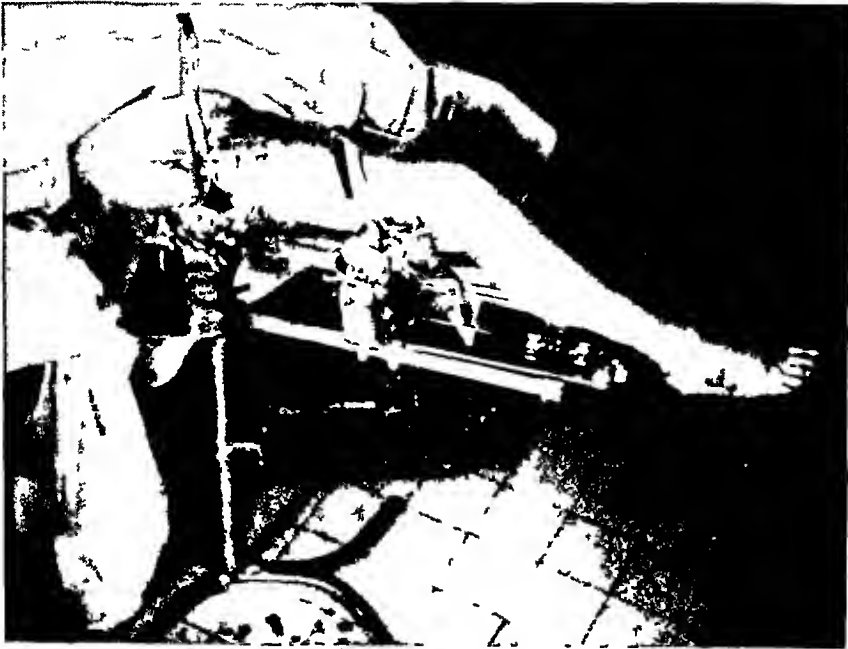


FIG 5b

FIG 5—a Reduction and fixation of a fractured femur with aid of anatomical  
splint

b Rods connected to fracture units

tension frame with five to ten pounds traction. The weight of the arm is usually sufficient for countertraction. If necessary the arm, just proximal to the flexed elbow, can be fixed to the frame with a sling over a piece of felt. When the desired position has been obtained a nonpadded narrow anterior and posterior moulded plaster splint reinforced with circular

plaster is applied from the shoulder to the distal crease in the palm for radial traction and to the proximal interphalangeal joints for metacarpal traction. Pyramids of plaster incorporate the protruding pin.

Before attempting to correct the overriding of the rotated major fragments, the simultaneous rotatory approximation of the major fragments must be coordinated with firm traction. Where spiral or oblique fractures are rotated so that their cortical surfaces are in apposition the reposition of the fractured surfaces must be effected before attempting traction.

While it is obviously desirable to obtain a perfect realignment of the fragments, a 50 to 75 per cent approximation of the fracture surfaces is

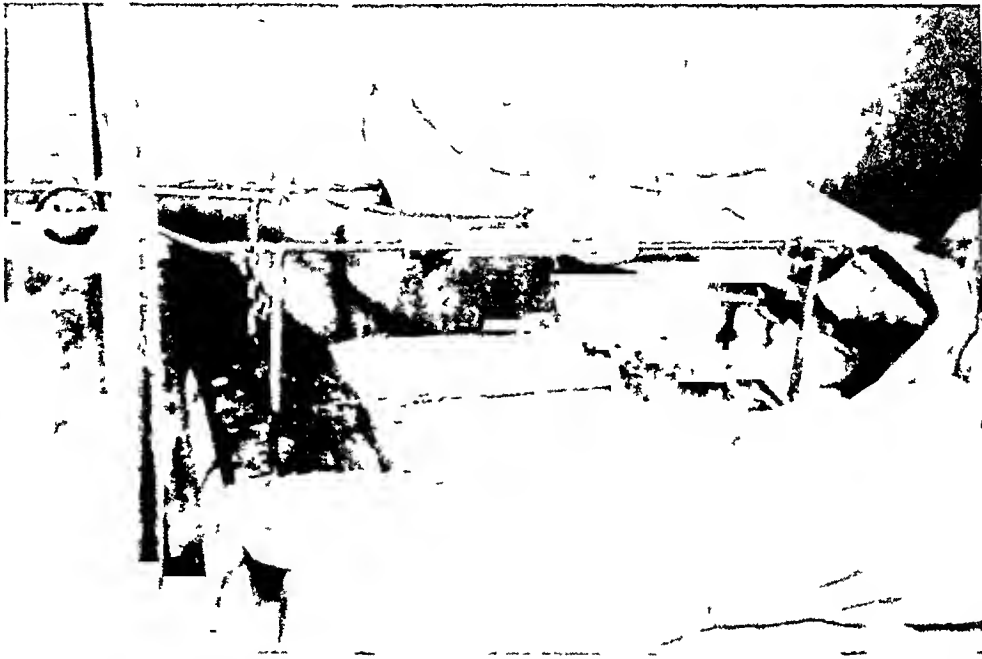


FIG 6—Boehler frame—through and through pin through tibia, two fingers' breadth above tip of internal malleolus, half pins inserted in sites of election. Ready for connecting rods, and application of moulded anteroposterior and circular encasement.

adequate if the rotation has been corrected and the proper long axis has been restored.

*Compound Fractures*—With the limb fixed in traction the débridement and the reduction is facilitated. Whenever it is possible the original traction should be maintained until the patient is placed on the operating table. If feasible before cleansing, no attempt should be made to correct the rotation of the fragments or to exert so much traction that a protruding fragment is drawn back into the wound. While maintaining traction, the site selected for the insertion of a traction pin is scrubbed with green soap, washed with ether and alcohol and painted with tincture of iodine and alcohol. The traction pin is inserted, a dressing and the caliper is applied. The traction cord is fixed to the traction bar or placed over the pulley on the splint with barely enough traction to hold the fragments in position.

Sterile gauze is again placed over the wound, the extremity is cleansed as outlined above. The wound is débrided and the desired number of pins are inserted into the major fragments. The pins are locked to their con-

necting rods The fragments are visually realigned into position by manipulating each fracture unit and exerting traction The connecting rod is applied and locked to both fracture units Where a self-aligning splint is available this procedure is greatly facilitated Sulfanilamide crystals are sprinkled into the wound and vaselined gauze is laid lightly across the wound A nonpadded encasement is then applied so as to adequately incorporate the adjacent joints The connecting rods may be left on the pins or small pyramids of plaster are applied to incorporate the projecting pins Subsequent changing of the plaster when necessary is facilitated by replacing the connecting rods This assures against redisplacement while applying a new encasement



FIG 7a

FIG 7b

FIG 7c

FIG 7—*a* Debrided compound fracture of the humerus and external half pin fixation, February 15, 1943  
*b* April 2, 1943—note extent of new bone formation  
*c* April 2, 1943—before removal of pins No infection of pin sites

The principles of Orr and Trueta having been so well established in the Spanish Civil War, in the present world conflict, and in civil surgery, that we believe it *obligatory to apply plaster to completely immobilize the extremity*, thus assuring the physiologic rest and lymphatic stasis necessary in the proper treatment of compound and infected wounds While we did successfully treat a compound fracture of the humerus without plaster, we do not believe repetition justified (Fig 7—*a*, *b* and *c*) The occasional successful case of compound fracture treated by external pin fixation without plaster will only serve to encourage others to use a procedure which is sure to prove disastrous and only serve to discredit it

### III — COMPLICATIONS

(1) *Infection—Prevention*—A discharge from the pin sites occurred in 37 cases (46 per cent) In many cases it was slight and was soon covered

with a crust, without actual suppuration. In some instances pus emanated from the bone and discharged for many months. In some cases the discharge persisted much longer than it required for the fracture site to heal (Figs 8, 9 and 14d). We believe that the infection of the pin sites is the most serious potential and real complication when using external pin transfixion of fractures. *The infection far transcends the dangers of distraction, delayed union and nonunion.* The latter does not endanger the lives



FIG 8



FIG 9

FIG 8—Note sequestrum in pin site, discharge persisted for more than a year.  
FIG 9—Fracture middle and lower third healed. Periostitis and large sequestrum subsequently removed from pin site.

of the patients and is more readily preventable or at least amenable to treatment with less hazard to the patient.

Most of our protracted infections and those that were fatal followed in those patients in whom the initial treatment did not include plaster.

To obviate external contamination of the pin sites as a source of infection we have been meticulous in our technic and have taken the precaution to seal over the pin sites. Nevertheless, we have seen what appeared to be an innocent nonsuppurative inflammatory exudate become purulent, extend along muscle and fascial planes, or into bone, and result in osteomyelitis. Or the infection may extend into the blood stream and may become fatal.

*Even the use of plaster does not mitigate against infection of the pin sites. When the swelling subsides the plaster may be wholly ineffective in mobilizing the soft tissues.*



**Case Report**—In the case of J D, who, on November 8, 1942, sustained a compound comminuted fracture of the tibia and the fibula, the wound had been debrided and the fragments transfixated with external pins and plaster. After having had a normal temperature for five days, it gradually reached 104° F on the 9th day. Chemotherapy was ineffective and it was subsequently discontinued to eliminate drug fever. Examination of the compound wound revealed no evidence of infection. However, the encasement was very loose around the pins and there was extensive suppuration about the pin sites which required multiple incisions. Culture of the pin sites revealed mixed pyogenic organisms and *Cl welchii*. Clinically, there was no evidence of gas gangrene. An encasement was reapplied. The patient's condition improved. In January, 1943, there was evidence of a metastatic involvement of the left acromioclavicular joint. Aspiration biopsy showed staphylococcus. Aspiration and immobilization in plaster was effective in controlling the pain and infective process. The pins were removed in two months, the pin sites healed in three months. Union was firm in seven months.

While the advantage of *ambulation* and early motion of joints would seem desirable, the inherent danger of infection of the soft tissue and bone from ambulation and unsupported soft tissue with plaster, is far too serious to recommend it as a routine procedure. *We believe that too much emphasis is laid on ambulation and joint motion.* The motion that accompanied the treatment of fractures of the femur with external fixation without plaster was not sufficient to justify subjecting these patients to the potential danger from infection. Only with the greatest difficulty could they be induced to get out of bed and use crutches. The friction of the pins against the soft tissues caused pain and a discharge at the pin sites in nine femoral fractures treated without plaster. Nor have we found that the ultimate restriction of the hip or knee after the use of plaster is any greater after the use of plaster than with the nonencasement treatment.

Certainly, in fractures of the tibia and fibula the desire of early motion of the knee or ankle is not a justifiable indication for the use of external pin fixation without plaster. In nine of the 54 fractures of the tibia and fibula we made a determined effort to use external pin fixation without plaster. After a few days the rigidity of the fragment could not be maintained. A discharge appeared at a pin site. While not always suppurative, its significance soon became apparent. Subsequent fixation of the extremity in plaster, from toes to the groin was necessary to limit the infection and to more rigidly fix the fragments and the pins. The mobility of the joints, while temporarily restricted in plaster invariably returned.

(2) *Distraction—Delayed Union—Prevention*—We attribute the mobility of the fracture site in cases which we treated without plaster to (1) ambulation and joint motion, (2) failure to properly transfix the fragments, (3) the elasticity of the pins (4) to the *pressure necrosis of the pins against the bone*, and (5) inadequate support of the soft tissues and pins with a short encasement. A pin became loose or the bone softened around the pin, and this impaired the stability of the fixation. As a result of the mobility of the fragments, decalcification of the fracture surfaces continued and a gap soon became apparent.

*Fractures of the Tibia and Fibula*—In our efforts to more rigidly trans-

# PIN TRANSFIXION OF FRACTURES

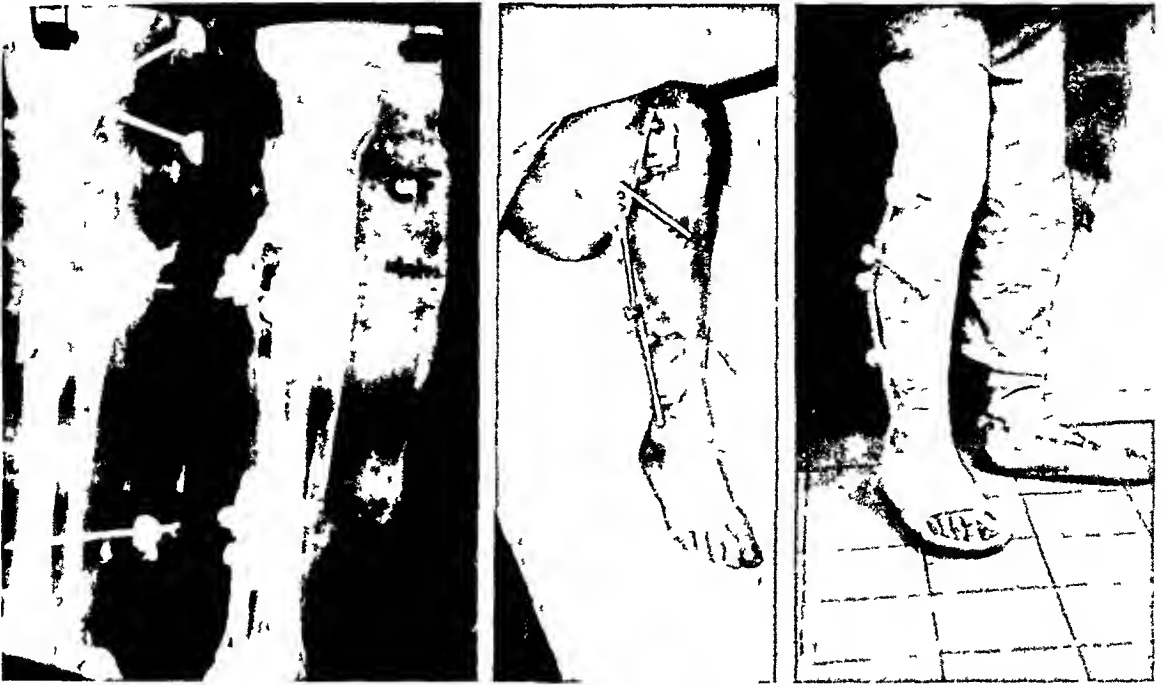


FIG 10a

FIG 10b

FIG 10c

FIG 10 —a Intermediate fragment transfixed and joined to connecting rods  
b External pin fixation—some mobility of fragments  
c Immobilization in plaster incorporating transfixion pins

FIG 11a

FIG 11b

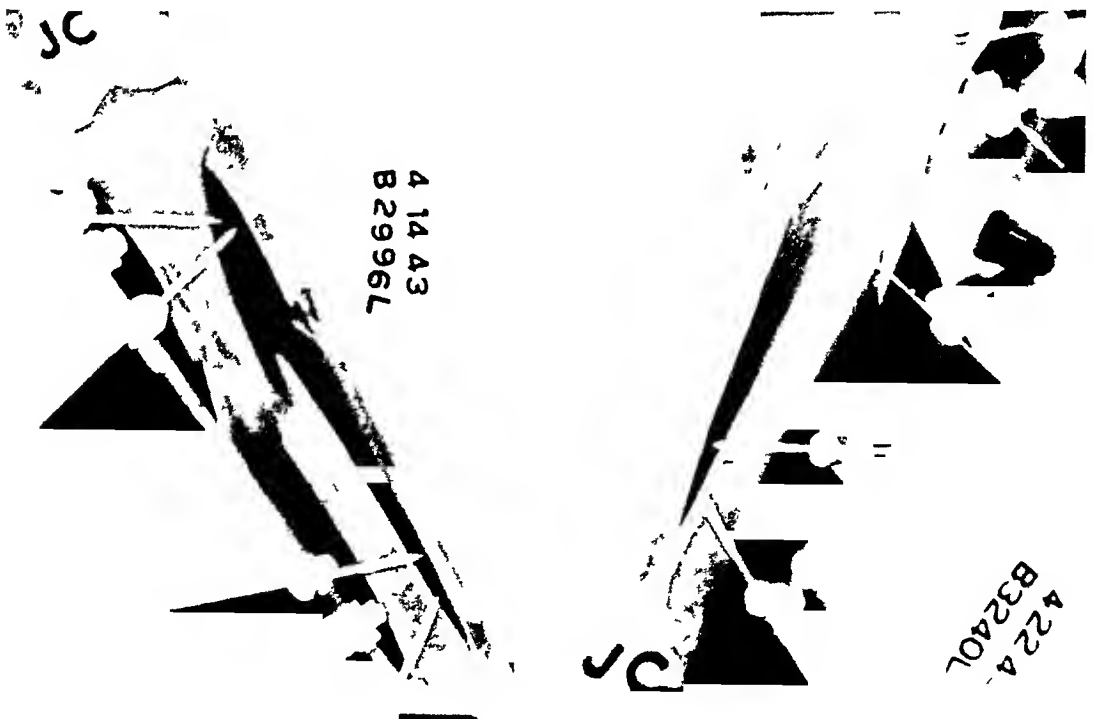


FIG 11 —Comminuted fracture tibia and fibula, April, 1943  
a Intermediate fragment slipped after transfixion of major fragments with Roger Anderson pins  
b Roentgenogram—transfixion of intermediate fragment

FIG 11c

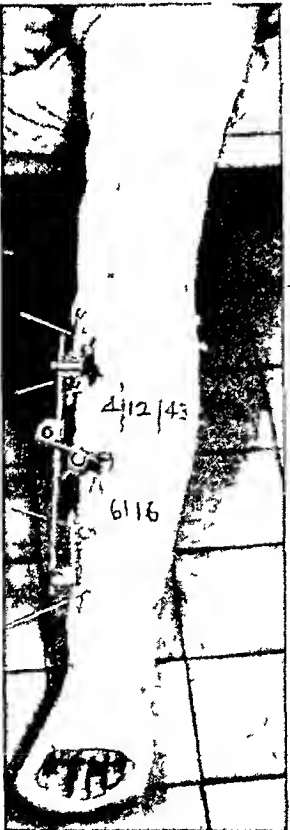


FIG 11d



FIG 11e

FIG 11—c Photograph of transfixion without plaster  
d Mobility of fragments necessitated the use of plaster  
e Roentgenogram December 9, 1943—evidence of union

## PIN TRANSFIXION OF FRACTURES

fix the major fragments without plaster we have employed a *transfixion pin across the fracture site* (Fig 10—a, b and c) In comminuted fractures an effort was made to *transfix the intermediate fragment* to one of the major fragments (Fig 11—a, b, c, d and e) We have also tried using four long through-and-through pins, the most proximal and distal pin being inserted at right angles to the longitudinal and transverse diameter of the tibia, while the others were inserted obliquely to the long and transverse axis of the



FIG 12

FIG 12—Four long through and through pins, the most proximal and distal pins are inserted at right angles to the longitudinal and transverse diameter of the tibia and the intermediate pins are inserted obliquely Pins fixed with two sets of rods Small plaster dressings applied around the pin sites

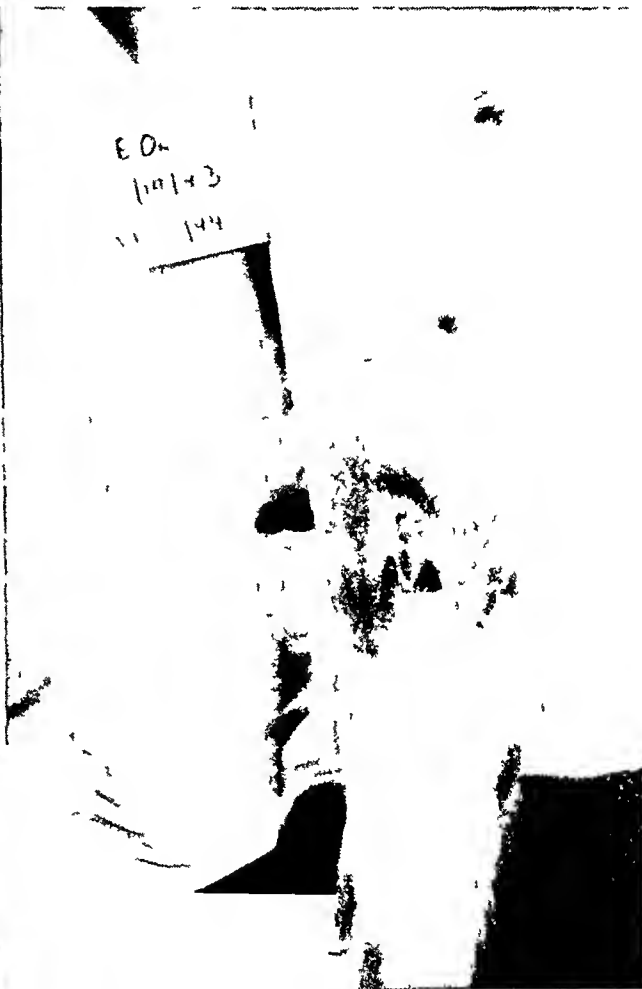


FIG 13

FIG 13—Showing excoriation around the pin sites one year after the pins were inserted

tibia (Fig 12) With none of these procedures was either sustained impaction or immobility of the fracture sites obtained without plaster The presence of long through-and-through pins, did not entirely eliminate the pressure necrosis and the softening of the bone around the pins or the infection at the site of the pin insertions (Fig 13)

*Application of Plaster*—In every instance of nonencased fixation of the fractures of the *tibia and fibula*, we had no alternative but to implement the fixation with plaster of paris, from the groin to the toes, and incorporate the pins in pyramids of plaster This more effectively maintained immobility of the fragments, with a minimal exudate and infection of the pin sites

*Early Removal of the Pins*—The practice of keeping pins in the fragments until there is roentgenographic or clinical evidence of union is a contributing factor to infection, maintenance of the fragments in distraction and causing delayed union. Early removal of the pins is definitely indicated, to prevent sustained distraction, prevent infection of the pin sites, and to permit the involuntary muscular contraction to approximate the decalcifying fracture surfaces, even at the expense of some alteration in the position of the fragments in a new skin snug-fitting encasement. Loosening the bars, or cutting a circular section out of the encasement or adjusting the turn buckle has not resulted in satisfactory impaction, in our hands. Wedging of the encasement is of inestimable value in correcting the bowing or angulation.

*Union of the tibia cannot keep pace with union of the vascularized muscular fractured fibula*. While the pins may not keep the fibula fragments from uniting, they do prevent the muscles from impacting the poorly vascularized comminuted tibial fragments or the partially decalcified transverse fractures, during the period of active hyperemia. If the pins are removed after the fibula has united and the tibial fragments are not in contact, union of the tibia will be delayed.

To obviate the possibility of delayed union due to distraction of the fragments by the pins and to prevent further friction of the pins in the loose encasement, the pins should be removed at the end of the 3rd or 4th week in transverse fractures and in the 5th or 6th week in spiral, oblique or comminuted fractures. The connecting rods are reapplied, the anterior two thirds of the shell removed and a snug fitting encasement from the groin to the toes is applied, with the knee in 30° flexion. After the encasement has hardened, the connecting rods are removed and roentgenograms are made. If the position of the fragments remained unchanged, the pins are extracted. Where there is a loss of bony structure in compound fractures—the pins should be maintained in position to maintain length until the wound is healed and the wound is ready for bone graft.

*Fractures of the Femur*—The problem of distraction and delayed union in fractures of the femur is not comparable to fractures of the tibia because of the ample blood supply to the femoral fragments. Distraction is a less serious concern in the oblique and spiral fractures because contact of the large fracture surfaces can be readily maintained. It is in this type of fracture that we had our most satisfactory results with the treatment without encasement.

It is in the cases of transverse and comminuted fractures that distraction with pins must be guarded against. The slightest movement resulting from the lack of immobility and sustained contact results in further decalcification of the fracture surfaces because of the continued hyperemia. A gap, which may be barely visible roentgenographically, may follow. This is in striking contrast to the large ossifying bony muscular hematoma which follows during the period of suspension with Russell traction. In Russell traction, the unopposed contracting muscles, which are one step ahead of any decalcification

which may result from shearing of the fragments, serves to impact the fractured surfaces

#### IV — INCIDENCE OF INFECTION OF PIN SITES — AND THE TIME REQUIRED FOR THE PIN SITES TO HEAL

The incidence of discharges from the pin sites is summarized in Table I. Thirty-seven of the 80 cases, or 46 per cent, developed some discharge, which varied from a slight serous exudate to a frank purulent discharge.

In 19 of the 37 cases, the discharge gradually diminished and the pin sites healed within one to eight weeks after the extraction of the pins. In 18, or 22.5 per cent, there was a low grade infection of the bone, from which, in some instances, a sequestrum was extracted.

*Fractures of the Humerus* — The pin sites, in three of the four simple fractures treated with external pin fixation, with a short plaster encasement, healed within two weeks after the extraction of the pins. There remained considerable edema and restriction of motion about the elbow for some time after the extraction of the pins in two cases.

In the compound fracture treated with external pin fixation, without plaster, there was no discharge or edema. The mobility of the shoulder and elbow was satisfactory during the period of transfixion and increased rapidly with the extraction of the pins.

Of the five fractures of the humerus treated by external pin fixation, the patient with the compound fracture, had the most satisfactory result as to freedom from pain, exudate and edema. The reason for the good result was first, the proper insertion of the pins at the sites of election, second, the firm transfixion of the pins through the fragments, and third, compound fractures of the upper extremity are more amenable to treatment than lower extremity injuries. Nevertheless, we do not advocate the nonencased treatment for compound fractures of the humerus.

*Fractures of the Tibia and Fibula* — Of the 54 simple and compound fractures, 16, or 29 per cent, developed an infection around the pin sites. In 12, or 22 per cent, an incision for drainage was necessary. Fourteen, or 26 per cent, developed an infection of the bone at the pin site.

Of the 31 simple fractures there was a discharge from the pin sites in ten, or 32 per cent. Incision and drainage was required in seven. The discharge persisted for three months in two, four months in two, five months in two, and four are discharging at the end of 13, 18, 18, and 21 months, respectively. Concentric sequestra was demonstrable in four, and roentgenographic evidence of an infectious process was ultimately evident in ten (Table II).

Of the 23 compound fractures, the pin sites discharged in six cases, or 26 per cent, and involved the bone in four. Incision and drainage was necessary in five. One patient, age 61, died in two and one-half months from cerebral thrombosis, pneumonia and cirrhosis of the liver and sepsis. The discharge persisted in one for three months, in two for four months, and in two for six months (Table III).

*Fractures of the Hip* — All seven of the fractures of the neck and inter-

TABLE II  
SIMPLE FRACTURE TIBIA AND FIBULA  
INCIDENCE OF INFECTION OF PIN SITES  
COMPARATIVE TIME FOR PIN SITES AND FRACTURE SITE TO HEAL

Case No	Age	Adm	Pins					Pin Site Infected	Time for Pin Site to Heal	Infection in Bone	Time for Fracture to Heal	Followed	No En- casement	Encase- ment
1	H B	46	2	3	4	5						7 mos		+
2	E B	69			+						4 mos	18 mos	+	+
3	I C	61			+			+	Disch 18 mos	Yes (S)†	5 mos	18 mos		+
4	H C	37			+						4 mos	20 mos		+
5	C F	47				+		+	Disch 5 mos	Yes	7 mos	18 mos		+
6	S F	55		+							6 mos	15 mos		+
7	S G	44	+								3 mos	13 mos		+
8	T H	60	+								4 mos	7 mos		+
9	S H	14		+							3 mos	6 mos		+
10	J H	42			+						9 mos	15 mos		+
11	M K	65		+				+	Disch 4 mos	Yes	3 mos	10 mos		+
12	J K	41		+				+	Disch 3 mos	Yes	5 mos	15 mos		+
13	J K	61			+			+			4 mos	13 mos	+	+
14	E K	42		+	+						5 mos	8 mos		+
15	E O	46		+	+			+	Disch 15 mos	Yes (S)	4 mos	15 mos		+
16	H P	63				+		+	Disch 4 mos	Yes	5 mos	16 mos		+
17	M O	41		+	+			+	Disch 5 mos	Yes	3 mos	15 mos		+
18	J S	53		+	+			+	Disch 21 mos	Yes (S)	14 mos	21 mos		+
19	A S	35		+	+			+			3 mos	16 mos		+
20	A S	35		+	+			+	Disch 18 mos	Yes (S)	3 mos	20 mos		+
21	J S	63		+							9 mos	12 mos		+
22	P P	53									3 mos	4 mos		+
23	J C	45				+					5 mos	8 mos	+	+
24	W L	45		+							4 mos	5 mos		+
25	F A	69			+						4 mos	10 mos		+
26	W F	50		+							4 mos	8 mos		+
27	J L	63						+	Disch 3 mos	Yes	4 mos	12 mos		+
28	H N	42		+							4 mos	12 mos		+
29	A O	47		+							4 mos	9 mos		+
30	M C	38		+							4 mos	6 mos		+
31	H H	56		+							6 mos	6 mos		+
Summary			3	6	18	4		10	7	10	4 (S)	7- 3 mos 13-4 mos	5	31
									4 disch					
									2 disch					
									2 disch					
									2 disch					
									5 mos					
									1- 7 mos					
									2- 9 mos					
									1-14 mos					

\* I &amp; D - Incision and drainage

† S - Sequestrum

PIN TRANSFIXION OF FRACTURES

TABLE III  
COMPOUND FRACTURE OF TIBIA AND FIBULA  
INCIDENCE OF INFECTION OF PIN SITES  
COMPARATIVE TIME FOR PIN SITES AND FRACTURE SITES TO HEAL

Case No	Age	Adm	Pins					Pin Site Infected	Sequestrum Pin Site	Pin Site to Heal	Without Encase	With Encase	Time for Fracture to Heal	Followed	Osteomyelitis Fracture Site
1 J B	52	11/42	+				+ I & D *	+	6 mos			+	7 mos	12 mos	+
2 A C	61	5/41		+			+ I & D		Died			+	Died—2 5 mos		
3 J C	30	7/41		+							2 mos	+	4 mos	8 mos	
4 J D	57	11/42			+		+ I & D		3 mos			+	7 mos	13 mos	+
5 W H	53	2/43			+		+	+	6 mos		2 mos	+	6 mos	12 mos	+
6 E L	58	12/41			+						1 mo	+	8 mos	2 yrs	+
7 H L.	57	9/42		+								+	7 mos	11 mos	
8 J R	57	6/42			+							+	19 mos	24 mos	
9 J S	30	12/42			+							+	3 mos	18 mos	
10 L S	45	11/42		+								+	4 mos	12 mos	
11 J S	50	7/41			+						2 mos	+	15 mos	20 mos	
12 W S	33	10/42	+									+	4 mos	14 mos	
13 J V	49	5/42		+								+	Ununited	2 yrs	
14 M W	39	1/42			+							+	2 yrs Bone graft	29 mos	+
15 E W	48	1/41	+									+	1 yr	20 mos	+
16 J Z	50	1/41	+				+ I & D	+	4 mos			+	3 yrs	3 5 yrs	+
17 M F	60	3/43			+							+	Ununited graft		
18 R L	43	1/43		+								+	3 mos	10 mos	
19 J O	51	3/43			+							+	11 mos	15 mos	
20 S R	20	1/43			+		+ I & D	+	4 mos			+	9 mos	10 mos	
21 F S	68	6/43			+							+	7 mos	10 mos	
22 B S	54	9/43			+							+	7 mos	9 mos	
23 M B	45	12/43	3	5	14	1	6 5	4	1-3 mos 2-4 mos 2-6 mos		4	+	5 mos	6 mos	+
Total												23	Under treat 3- 6 mos —7 7-12 mos —9 15-19 mos —2 Ununited 3		8 (old)

\* I & D —Incision and drainage



trochanteric region treated by external pin fixation without plaster developed some discharge at the site of the pin insertion. Every effort was made to keep the pin sites meticulously clean. Five patients subsequently developed general sepsis and died. The discharge from the other two ceased in a few days after extracting the pins.

External pin fixation without plaster for fractures about the hip is a hazardous procedure. If a plaster spica is applied to implement external pin fixation in elderly people, we would be reverting back to chaining the patient to the mattress, with its potential complications. In a report, on "Fractures of the Neck of the Femur. An Analysis of 157 Cases," we stated that other than expediting the procedure of immediate transfixion and minimizing the trauma in the process of fixation, external pin fixation had no advantage over internal fixation. The incidence of infection and sepsis was too high, the nursing care was increased, and the patients were apprehensive and refused to be ambulatory because of the pain in the region of the pin sites. There was a constant dread of infection. The patient could not be discharged from the hospital with the protruding apparatus. The uniformly good results with internal fixation of fractures about the hip, does not justify subjecting patients to the hazards of external pin fixation.

*Fractures of the Shaft of the Femur*—Nine of the 12 simple fractures, or 75 per cent, developed a discharge from one or more of the pin sites (Table IV). In five the pin sites healed within a few days, or weeks, after extraction of the pins. One discharged for one month, one for seven months, one for eight months, and another for 13 months. In three there was a destructive bony process at the pin sites, in two of whom a sequestrum was removed.

In three instances, the pins were extracted before union was complete because of an infection of the pin sites. The extremities then were suspended in Russell traction. No redisplacement of the fragments resulted. In one, the infection subsided with the removal of the pins. In another it required seven months after sequestrectomy and immobilization in a plaster spica, and penicillin, to control the infection. In the third (M. H., age 76) there was a low grade destructive process in the bone at the distal pin site. Eight months after the original fracture she sustained a fracture through the discharging distal pin site below the healed original fracture site. She died several days later from pulmonary embolism.

#### V — RELATION OF THE HEALING TIME OF THE FRACTURE SITE TO THE TIME REQUIRED FOR THE PIN SITES TO HEAL

As shown in Tables II, III, and IV, the pin sites continued to drain in many cases as long as it took the fracture to heal. In some instances the pin sites drained long after the fracture was united.

There were five simple fractures of the tibia and fibula which continued to drain with a variable amount of edema and excoriation after the fracture site healed. Two fractures which were healed in three months continued to drain, one for five months and the other for 16 months, another was healed

PIN TRANSFIXION OF FRACTURES

TABLE IV  
FRACTURES OF THE FEMUR  
INCIDENCE OF INFECTION OF PIN SITES  
COMPARATIVE TIME FOR PIN SITES AND FRACTURE SITES TO HEAL

Case No	Age	Adm	Pins	Pin Fixation		Subsequent Treatment	Operation and Pin Fixation	Discharge from Pin Site	Time for Pin Site to Heal	Time for Fracture to Heal	Followed
				No Encase	Encase						
1 M H	76	5/43	+	4 mos short	Encase	Russell Traction 2 mos		Osteomyelitis—fracture through pin site—8 mos	Discharged until death at 8 mos	6 mos	Died Pulmonary embolism
2 R L	52	11/43	+	18 days		3 mos	Encase 11 mos	Osteomyelitis 13 mos	7 mos	4 mos	7 mos
3 S C	59	2/43	+	5 wks.		3 mos	Osteomyelitis 9th month	Osteomyelitis Yes (I & D)	13 mos (I & D)	9 mos (Osteomyelitis)	14 mos
4 R D	35	1/43	+	4 mos		Encase 5 mos—then	Dual onlay graft—Haynes pins—no union		Few days	1 1/2 mos (Osteomyelitis)—graft	15 mos
5 T D	48	12/42	+	3 mos				Yes	Few days	4 mos	6 mos
6 J G	57	8/42	+		Spica 4 mos			Yes	Few days	4 mos	15 mos
7 M J	28	12/42	+	3 mos				Yes	2 wks	4 mos	4 mos
8 P P	49	8/42	+	3 mos				No		4 mos	15 mos
9 E R	55	3/43	+	3 mos			No encase	Yes I & D	Few days	4 mos	9 mos
10 A T	105	10/42	+	2 days							Died—2 days
11 K Mc	51	5/42	+		Spica 4 mos	2 mos		No		4 mos	14 mos
12 J Mc	58	9/43	+	2 mos short				Yes	1 mo	4 mos	6 mos
13 J H	56	10/43	+		Spica 5 wks		Débridement	Yes			Died Multiple injuries
Total			1 6 6	10	3						10

in 14 months, and drained 17 months. Two fractures were healed in four months and drained, one for 13 and the other for 15 months. Five others continued to drain about as long as it required for the fracture to heal, in two cases the pin sites drained for three months, and the fracture was healed in four months, in two others the pin sites drained for four months, and the fracture was healed in five months, while one pin site drained for seven months, and the fracture site healed in seven months.

In the compound tibial fractures, the pin sites healed before the fracture sites. In one, the pin site drained for three months, two drained for four months, and two for six months. Many of these fractures were extensively comminuted, there was less manipulation, less trauma at the pin sites and in most instances they were immediately immobilized in plaster, to which, we attribute the earlier healing of the pin sites.

The pin sites in three of the cases of fractured femur continued to discharge long after the fractures were healed. One was discharging at the end of eight months, two months after the fracture had healed, when the patient sustained a new fracture which extended through the discharging distal pin site below the original healed fracture site. In another patient, the discharge from a pin site persisted for seven months, which was three months after there was roentgenographic and clinical evidence of union of the fracture site. The third case, a badly comminuted fracture was united at the end of nine months but continued to drain for another four months from the proximal pin site from where a sequestrum had been partially removed.

#### VI — TIME REQUIRED FOR HEALING OF FRACTURES TREATED BY EXTERNAL PIN FIXATION

In evaluating the time required for the healing of fractures treated by external pin fixation it would be desirable to compare the time required to heal a similar group of cases treated by other procedures. Watson Jones and Coltart have recently reported the results of their treatment of fractures by various procedures. From our experience we are fully in accord with these observers that external pin fixation is a contributing factor in delaying union by maintaining the fragments in distraction.

It is obviously difficult to evaluate reports of the treatment of fractures. Most of the fractures we are reporting were badly comminuted and in individuals past 45 years of age. There is one very pertinent factor which we have observed in reviewing our cases, namely, that the less additional trauma we inflict on the fractured limb the sooner will the fracture unite. Our best results with femoral shaft fractures have followed with Russell traction. While in fractures of the tibia and fibula, the Kirschner wire in the os calcis, Bohler frame and plaster has given us our most satisfactory results.

Union followed in the majority of femoral shaft fractures in three to four months, unsupported weight bearing had to be guarded for another four to eight weeks. Because of pain in the region of the pin sites, it was with great reluctance that some of the patients could be gotten out of bed to

become ambulatory and move their joints. When plaster was used with the pins the mobility of the joint was equally slow in returning. This is in striking contrast to those cases treated in Russell traction. Russell traction was generally discontinued in two to three months. Quadriceps exercises were instituted soon after the traction was applied. Ambulation with crutches was permitted soon after discontinuing traction and the range of mobility of the joints was generally satisfactory at the end of the fourth month when in many cases crutches could be dispensed with.



FIG 14a



FIG 14b



FIG 14c

FIG 14—*a* Roentgenogram on February 26, 1943—note comminution and rotation of intermediate fragment

*b* April 26, 1943—fixation with half pins—open operation, impaction of major fragments, note sequestrum in distal pin site of the proximal fragment

*c* March 3, 1944—another sequestrum still present at fracture and pin sites

The high incidence of slow union in tibial fractures was most noticeable in the cases in which the pins were left in for two months, or longer. This has become less apparent with the early removal of the pins and continued immobilization from toes to groin plaster with the knee in 30° flexion. Of the simple fractures, seven healed in three months, 13 in four months, five in five months, one in six months, one in seven months, two in nine months and one in 14 months. In the compound fractures slow union was particularly noticeable, seven united in from three to six months, nine required seven to 12 months, two from 15 to 19 months and three were ununited fractures at the end of two years, two of which were grafted.

#### VII—INCIDENCE OF INFECTION OF THE FRACTURE SITE FOLLOWING OPEN OPERATION WITH EXTERNAL PIN FIXATION WITHOUT PLASTER

*Femurs*—In three patients, because of the persistent displacement, the fracture site was exposed and the fragments were transfixed with fracture units without plaster.

In one patient (Case 3) an infection developed at the fracture and pin sites. Sequestra were incompletely removed and the discharge persisted.

FIG 15a

FIG 15b



FIG 15c

FIG 15d

FIG 15—*a* Retouched negative showing extent of displacement of proximal fragment and comminution on admission March 11, 1943

*b* April 6, 1943—after transfixion of major and intermediate fragments

*c* Reduction on Hawley table—note extra connecting rods

*d* December 10, 1943—extent of union nine months later

from both sites for 13 months although the fracture site has been firm for four months (Fig 14—*a*, *b* and *c*) In another patient (Case 9) an infection of the site of the incision healed within a few days after the pus was evacuated (Fig 15—*a*, *b*, *c* and *d*) The third patient (Case 4) was admitted from another institution, three months after the injury, with an ununited comminuted fracture This had previously been fixed with three Parham bands The bands were removed and the fragments were transfixed with Roger Anderson fracture units One month later two Steinman nails were inserted

into the fractured neck of the femur and connected to the proximal fracture unit. An infection developed in the region of the pins that were inserted into the hip. The infection healed in a few days after extracting the hip pins. Four months after transfixion of the shaft of the femur the pins were removed. There was no evidence of union of the major fragments. A plaster spica was applied. Five months later there was still no evidence of union. A dual onlay graft was fixed to the major fragments with vitalium screws and the fragments were transfixed with Haynes pins, without plaster. Five months

FIG 16a

FIG 16b

FIG 16c



FIG 16—a Injury October 27, 1942. Transferred to Bellevue Hospital January 23, 1943—with Parham bands and plaster.  
b Parham bands removed January 29, 1943—nonunion, distal major and intermediate fragments transfixed with aid of Roger Anderson anatomical splint.  
c October 2, 1943—distal fragment ununited.

later the Haynes pins were removed. There was evidence of union. There was no discharge from the pin sites during the five months. There was, however, a low grade infection of the wound. Two months later the vitalium screws and a small devitalized fragment of the graft were removed. The screw sites were clean. The wound was treated with penicillin locally and penicillin was given intramuscularly. Fourteen days later the wound was practically healed (Fig 16—a, b, c, d, e and f).

*Humerus*—External pin fixation units were used on an ununited fracture of the middle and lower third of the humerus in a man, 38 years of age. He sustained the fracture in January, 1943. He was plated in Africa the same day. In June he was admitted with a gap between the fragments. The Lane plate was removed, an onlay graft was fixed to the fragments with vitalium screws. The fragments were also transfixed with Roger Anderson pin units and the extremity was incorporated in plaster. The pins were removed in ten weeks because of some edema about the distal pin sites. This

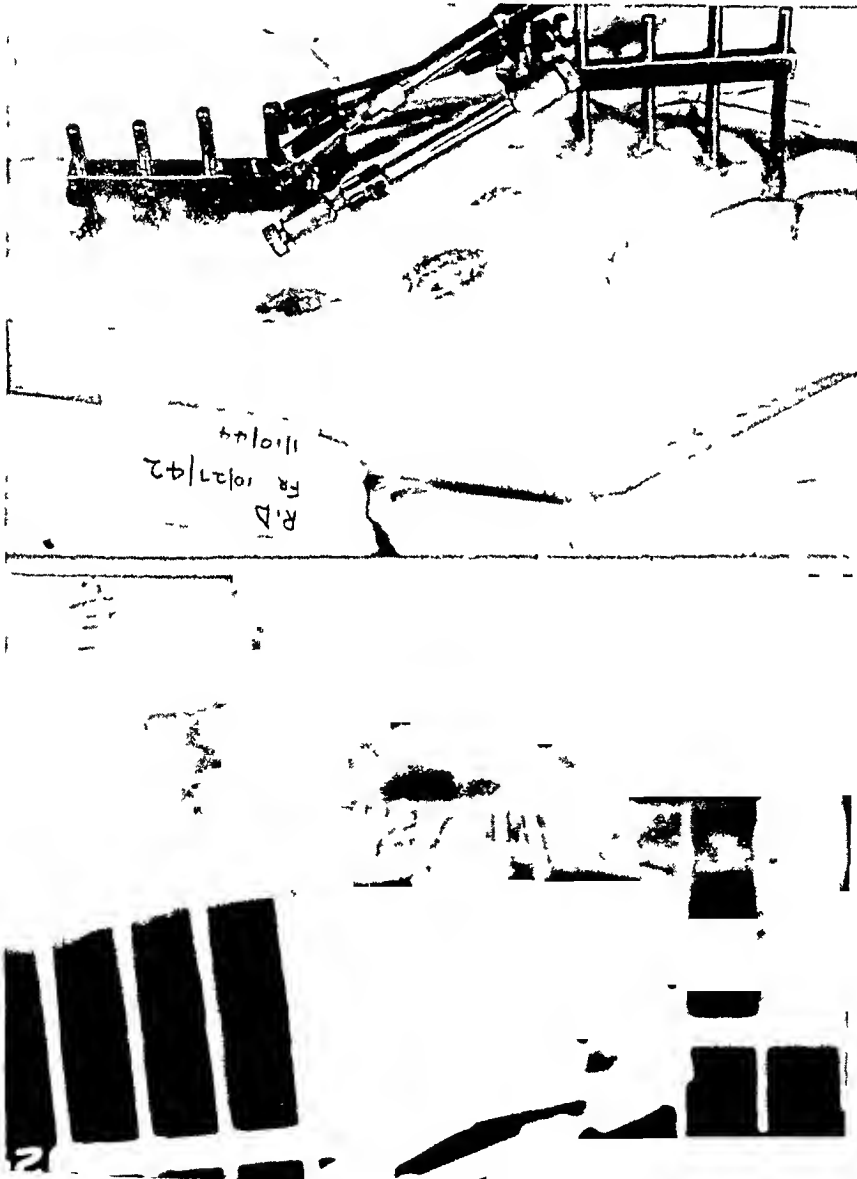


FIG 16d

FIG 16c

FIG 16f

FIG 16—d and e Roentgenogram and photograph in January, 1944 Dual onlay grafts, vitalium screws Haynes pins applied October 10, 1943 Slight discharge from wound Pin sites clean Pin sites clean clinical and radiographic evidence of union Very slight discharge from operative incision April, 1944 Pins removed March 21, 1944 Pin sites clean Small fragment of graft necrotic removed Fracture healed Penicillin locally and intramuscularly June 2, 1944, screws removed, sites clean June 12—slight discharge

disappeared with the removal of the pins Union was firm in four months No infection developed He has been followed one year (Fig 17—a, b and c)

COMMENT—After an open reduction for a fracture of a long bone and transfixion of the fragments with pins, a plaster encasement adequately immobilizing the extremity should be applied

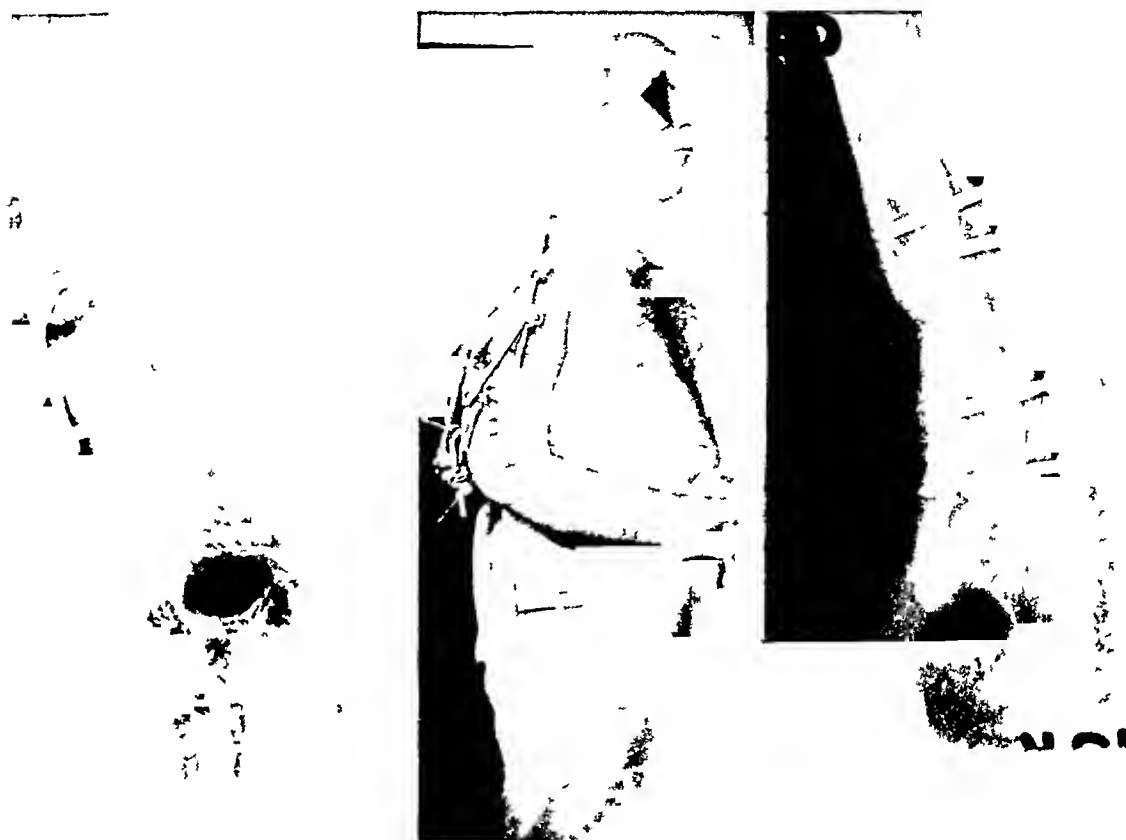


FIG 17a

FIG 17b

FIG 17c

FIG 17—Case F P, age 38 Fractured humerus plated, in Africa, June 22, 1943  
a Roentgenogram June 10, 1943—nonunion—Lane plate holding fragments in distraction  
b Photograph September 23, 1943 after removal of Lane plate and insertion of onlay graft  
Vitalium screws and external pin fixation with Roger Anderson fracture units  
c December 20, 1943—six months later—extent of union

When a bone is grafted and the graft is transfixed with vitalium screws, it is imperative that a plaster encasement be applied to adequately immobilize the extremity External pins, for the purpose of increasing the stability of the fragments, introduces a potential hazard, which should be avoided

#### VIII — INDICATIONS FOR THE USE OF EXTERNAL PIN FIXATION

External pin fixation with or without plaster is not indicated when a more conservative procedure can be used which will give a good clinical result without subjecting the patient to the potential complications of external pin fixation

(1) *In selected problem compound fractures* when, in the surgeon's opinion, immobilization in plaster or distal pin traction and plaster, will not maintain a satisfactory realignment of the fragments, then, the procedure may be used with plaster adequately immobilizing the extremity (Fig 18—a, b, c and d)

(2) *In infected fractures with persistent displacement* to realign the



Fig 18a



Fig 18b

Fig 18c

Fig 18d

Fig 18—a Patient age 50 Admitted, July, 1941, in shock, stupor, fractured ribs, dislocated left elbow, subluxation of right knee, Colles's fracture and a compound fracture of the lower third of the left tibia and fibula—treated for shock—transfixion pins without anesthesia, no debridement, sulfanilamide crystals

b Roentgenogram on admission

c Transfixion pins and plaster

d Roentgenogram March 6, 1943—firm union

# PIN TRANSFIXION OF FRACTURES

FIG 19a

FIG 19b



FIG 19c

FIG 19d

FIG 19—a Patient age 39 Sustained a compound fracture of the middle third of the left tibia and fibula on January 1, 1942 Admitted to Bellevue Hospital January 31, 1942 Roentgenogram on February 1, 1942—one inch of overriding tibia protruding through infected wound

b Roentgenogram May 25, 1942 after realignment with Roger Anderson pins and anatomical splint—sequestrum of proximal end of distal tibial fragment

c Roentgenogram October 15, 1943—sclerotic ends of bone six months after wound was healed

d Roentgenogram showing dual onlay bone graft and vitalium screws Encasement removed April 1944—firm union Very slight discharge Screws out May, 1944 June, 1944, wound healed

fragments and to maintain them in position with the aid of plaster until there is sufficient union to permit the extraction of the pins (Fig 19—a, b, c and d)

(3) *In compound and infected fractures*, in which there is a loss of bone external pin fixation and plaster can be used to maintain length until the wound has been healed sufficiently long to permit the insertion of a bone graft

(4) (a) *Simple fractures* Mechanical pin fixation with plaster may be used when conservative treatment fails to adequately correct rotation, restore



FIG 20a

FIG 20b

FIG 20—a Half pins for spiral and oblique fracture of the femur  
b Half pins in the proximal fragment, two through and through pins in the low supra condylar fragment and a transfixion pin in the lower end of the proximal fragment

the proper long axis of the fragments, approximate some of the fracture surfaces of a transverse fracture or approximate a displaced intermediate fragment

(b) *Simple fractures of the shaft of the femur*, external pin fixation without plaster, or with a short encasement, permitting ambulation on crutches, may be employed only *with the patient fully aware of the potential hazards* and the surgeon is thoroughly familiar with the procedure (Fig 20—a and b)

#### CONCLUSIONS

In 80 cases of external mechanical pin fixation of fractures the high incidence of discharge from the pin sites (46 per cent), of osteomyelitis of

the pin sites with persistence of discharge long after the fracture had united (22.5 per cent), and of deaths (10 per cent) should preclude the further use of the method as a routine procedure for fractures of the long bones and of the neck of the femur. The procedure should be used only in selected cases and by those who have been specially trained in the technique.

The potential dangers, of infection of the sites of the pin insertions, far transcends the dangers of distraction, delayed union and nonunion. The latter does not endanger the lives of the patients and is more readily preventable and amenable to treatment.

It should be restricted to certain problem fractures and to persistently displaced compound fractures, in which, by visual manipulation, the reduction can be facilitated and maintained, until a properly fitting encasement can be expected to maintain the realignment of the fragments.

Too much emphasis has been laid on ambulation and joint motion. Ambulation and early mobilization of joints should not be the motivating factors for the use of external mechanical pin fixation.

Infection of the pin sites and distraction and delayed union are attributed to (1) ambulation and motion of joints without plaster, (2) friction of the soft tissues against a pin which causes the infection and osteomyelitis, (3) *pressure necrosis* of the bone by a pin which impairs the stability of the fixation, permitting a continuous hyperemia of the fracture site with absorption of the ends of the bone, resulting in distraction of fragments, (4) the prolonged use of the pins, (5) failure to immobilize adequately the extremity and pins in plaster, and (6) failure to reapply a snugger encasement when the swelling subsides.

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## BOOK REVIEW

INTRACRANIAL ARTERIAL ANEURYSMS By Walter E Dandy, Adjunct Professor of Surgery in The Johns Hopkins University Pp 147 Ithaca Comstock Publishing Company, Inc, Cornell University, (1944)

This study is based on 108 cases of intracranial aneurysms Of these, 44 were postmortem findings over a period of 50 years The 64 cases disclosed at operation cover a period of 20 years However, it is only a little over six years since the first planned operation for an aneurysm was carried out by the author Since that time 36 aneurysms have been exposed at operation, all but three having been correctly diagnosed preoperatively In 30 cases an attempt at surgical treatment was made, with resulting cures in 70 per cent

Based on his experience the author found that the most favorable site for surgical treatment was the intracranial portion of the carotid prior to its branching

A chapter on the development of the circle of Willis, by Dorcas Hager Padget, helps not only in the understanding of the site of origin of some of the aneurysms but sheds light on the possibility of untoward results following ligations Because of frequent anomalies the remaining patent branches may be inadequate

Informative tables of cases grouped on the basis of the vessel involved, an extensive bibliography and excellent illustrations round out this presentation of the author's experiences in a seldom trod path in neurologic surgery

IRA COHEN, M D

**STATEMENT OF THE OWNERSHIP, MANAGEMENT, CIRCULATION, ETC, REQUIRED BY THE ACTS OF CONGRESS OF AUGUST 24, 1912, AND MARCH 3, 1933 OF ANNALS OF SURGERY, published monthly at Philadelphia, Pa, as of December 1, 1944**

State of Pennsylvania } ss  
County of Philadelphia }

Before me, a Notary Public in and for the State and county aforesaid, personally appeared Ellis W Bacon, who, having been duly sworn according to law, deposes and says that he is the Treasurer of the ANNALS OF SURGERY and that the following is, to the best of his knowledge and belief, a true statement of the ownership, management (and if a daily paper, the circulation), etc, of the aforesaid publication for the date shown in the above caption, required by the Act of August 24, 1912, as amended by the Act of March 3, 1933, embodied in section 537, Postal Laws and Regulations, printed on the reverse of this form, to wit:

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[Signed] ELLIS W BACON

Affirmed to and subscribed before me this 18th day of October, 1944

[Seal]

LILLIAN I LIVINGSTON

(My commission expires February 9, 1947)

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